Nearly Neutral Allylation of Oxygen Nucleophiles

An Honors Thesis (HONRS 499)

By

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Thesis Advisor

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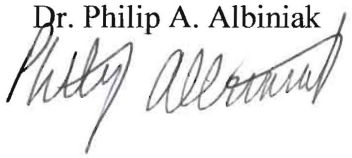

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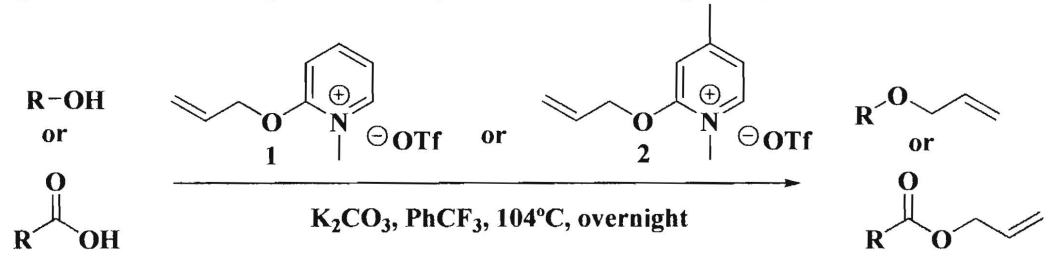
Abstract

The following document describes a qualitative investigation into the ability of 2-allyloxy-1-methylpyridinium trifluoromethanesulfonate (AOPT) **(1)** and derivatives to form allyl esters and ethers under mildly basic conditions **(Scheme 1)**. These ester and ether moieties are useful to protection chemistry and are very common in biological synthesis of large molecules.



Scheme 1

Results show that **1** was successful as an allylating reagent under mild conditions, 2-allyloxy-1,4-dimethylquinolinium trifluoromethanesulfonate (AOdMQT) **(2)** was also successful. Optimal conditions as determined in this study for performing each reaction are found in the discussion, along with reasoning and motivation toward each change.

Acknowledgements

- Dr. Philip A. Albiniak, my thesis advisor, for the opportunity and support
- Ball State University
- Ball State Department of Chemistry
- Ball state Honors College
- CRISP Program
- Honors College Undergraduate research Fellowship for funding

Author's Statement

The subject of my thesis is the research I have been doing under Dr. Albiniak of the Ball State Department of Chemistry since spring semester 2013. I have been working to develop a reagent capable of falling apart when heated (thermolysis) to give a reactive allyl cation without the use of strong acid or base catalysts. This is of great benefit to synthetic chemistry because it widens the range of substrates that this reactive allyl cation can be installed upon, which in turn opens up new possibilities for pharmaceutical and biological molecular synthesis. Details and examples supporting both claims are within the document, along with experimental evidence and proof of success.

The research has taught me a lot about developing new scientific literature and methodology, as well as increasing my laboratory skill set. The experiment was created and changed with a systematic approach using scientific methods and careful record keeping. Details of the decisions made, reasoning behind those decisions, and motivation for pursuing this study are also given in the document.

Writing the document has drastically increased my comprehension of scientific literature and familiarized me with journals and resources that will enable me to independently find answers to problems and implement the discoveries of others in pursuit of my own work. I have often been told by my professors that the true skill I have been learning is problem solving, and this new knowledge has dramatically increased my ability to find answers to my own problems and questions. The first chapter of this document is a literature review with other examples of the same chemical reaction as well as a review of the scientific importance of the chemistry being developed. This chapter and the accompanying sources in the references section of the document will serve to illustrate this point.

The document features a lot of scientific language and graphical representations. The work is in organic chemistry and we chemists like to express our ideas in picture form. The document contains many picture forms of chemical equation and molecular structure. Explanations of the importance of each image are included in the document. Regrettably, these can only be simplified or generalized so far without losing meaning. I feel I have done what I can within the document by using colors and arrows to indicate important features.

Best of luck reading the document, I really hope you manage. It represents a lot of hard work.

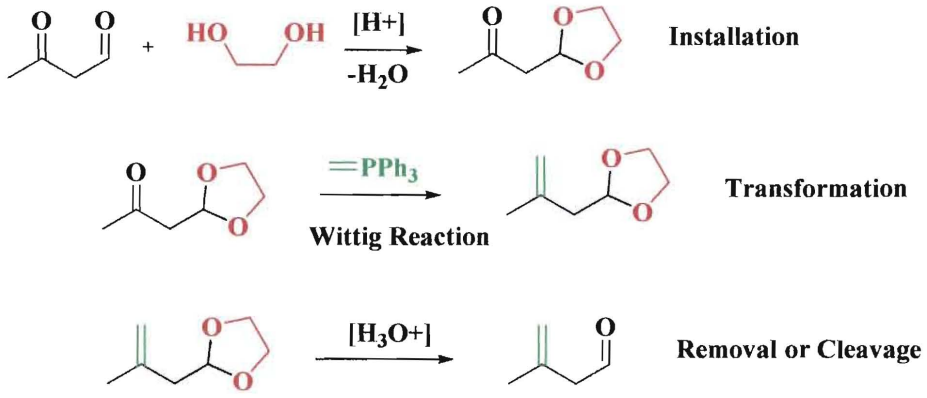
Matthew H. Bunner

Contents

Introduction: Theory of Protection Chemistry

A common difficulty in the synthesis of increasingly complex molecules is the presence of multiple sites with the same reactivity at each stage in the process. To achieve the desired transformation, reactive sites that are to remain unchanged must be blocked.[1] The reagents used to block other reactive sites are called protection groups or protective groups. The continually increasing complexity of synthetic chemistry demands the development of better and better protective groups to achieve the desired regio-, sterio-, and enantio-selective transformations under conditions that will not compromise the material being transformed. New and more satisfactory protective groups, and methods of utilizing those protective groups, are constantly being developed to enable the synthesis of natural and unnatural products that were previously unattainable due to their complexity.[1]

Protection chemistry has three major steps: installation, where the protection group masks the target site; transformation, where the desired change is made to a molecule and the protected site is unchanged; and removal, where the protection group is removed and the masked site is restored to previous functionality. The example below **(Scheme 2)** shows a Wittig reaction with (installation, transformation and removal steps) and without (unprotected step) a type of protection for carbonyls called acetal formation. Formation of the acetal favors masking the aldehyde over the ketone because the carbon in question is less hindered and more electrophilic. This ability to select protected sites is vital to protection chemistry.



Scheme 2

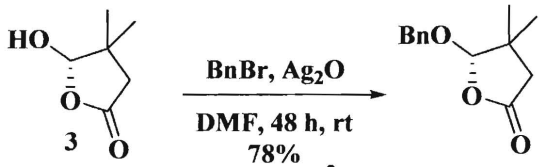
The installation and removal steps have the same goals for "effective" protection chemistry: reactions must be fast, efficient, and must not change and other sites of the molecule. High yields are especially important for the installation and removal steps because these steps are lateral movements in a synthesis instead of steps forward. That is, installation and removal of protection groups to not advance an overall synthesis any closer to the goal. The transformation step must allow the desired transformation to occur without interference from the installed protection group while protecting the masked site from any changes. The protection group should also be devoid of any additional functional sites and should not exert any electronic influence on the masked molecule. Because of these strict requirements, the development of protective groups and methodology is a challenging field and development of an efficient material and method for protection is a significant achievement.

Chapter 1: 2-Benzyloxy-1-methlpyridinium Trifluoromethanesulfonate (BnOPT)

1.1 Benzyl Ethers and Esters

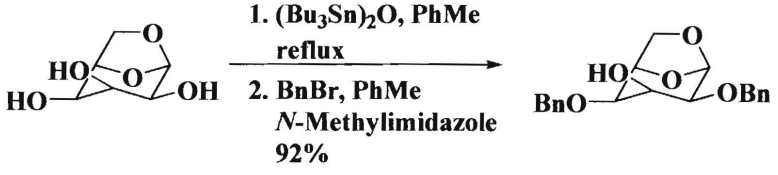
The benzyl group is a good protective group for synthesizing benzyl ethers and esters by masking alcohols and carboxylic acids. The benzyl group imparts little electric influence and contains little competing reactivity.[1] Benzyl groups are particularly versatile owing to the variety of mild cleavage reactions for the removal step.[2] The ease of cleavage does lead to some trouble, as strong acid or base conditions can remove the benzyl group before the intended time, giving a small drawback to limitation imposed by conditions in the transformation step.[1]The benzyl protection group does suffer from another drawback, it's a bulky piece to attach to a molecule. So, while useful for many syntheses of unhindered products, the use of benzyl ethers or esters is not recommended for syntheses of complex natural products and their derivatives due to the amount of hindrance such compounds contain.

The following are some recently developed methods of installing benzyl protective groups under mild conditions. Some, like the reaction of benzyl halide and free alcohol in the presence of silver oxide **(Scheme 3)**, also provide unique results that are very useful in synthetic chemistry.



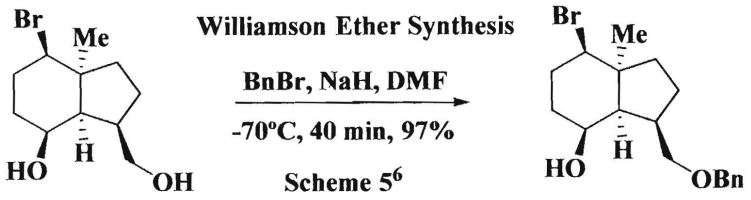
Scheme 3[2]

The oxygen of the primary alcohol is exclusively benzylated without any loss or change to the lactone when 5-methoxy-4,4-dimethyl-2(3H)-furanone **(3)** reacts with benzyl bromide in the presence of silver oxide **(Scheme 3)**.[2] This method was developed in a previous paper,[3] but the utility was not discovered until it was used to perform the reaction above when all other methods failed.



Scheme 4[4]

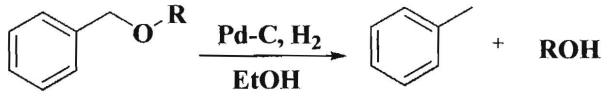
Equatorial hydroxyl groups are protected preferentially to axial groups in the reaction shown above **(Scheme 4)**.[4] Tributyltin oxide reacts with hydroxyl groups to give a stannylated oxygen species which mediated the benzylation when presented with an electrophilic benzyl synthon.[4] Tributyltin oxide can also be used to cleave carboxylic esters.[4] Both uses rely on principles of hard-soft acid base chemistry, so substrates much be chosen accordingly.[5]



Scheme 5[6]

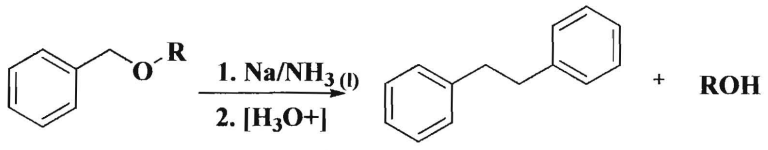
Exclusive benzylation of a primary alcohol can be achieved at -70℃ by reacting with benzyl bromide in the presence of sodium hydride **(Scheme 5)**.[6] This reaction is an example of a Williamson ether synthesis. The low energy due to temperature and the difference in reactivity between primary and secondary alcohols additively contribute to the selectiveness of this reaction.

One of it's the greatest benefits of the benzyl protective group is its propensity for mild methods o selective cleavage. Cleavage by palladium catalyzed hydrogenolysis is particularly mild and successful **(Scheme 6)**.[7] Palladium is preferred over platinum to avoid reducing aromatic rings.[1]



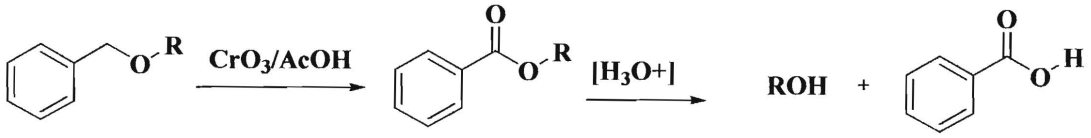
Scheme 6[7]

Another possible method of cleavage is single electron reduction using dry sodium metal and liquid ammonia.[8] The benzyl protection group is removed as bibenzyl and the protected reagent can be quenched with a proton source in a second step **(Scheme 7)**.



Scheme 7[8]

Oxidative methods of cleavage can also be used for substrates that are sensitive to hydrogenolysis or dissolved metal. The method shone in **Scheme 8** was used successfully on carbohydrates with such sensitivities.[9] Esters are stable to this method, but glycosides and acetals are also cleaved.[9]



50%

Scheme 8[9]

Generic schemes of two common benzylation reactions, Williamson ether synthesis and protonating trichloroacetimidates, are shown below **(Figure 1)**. Benzyl esters can be prepared from many of the common methods of generating esters, such as reacting an acid halide or anhydride with benzyl alcohol in the presence of a catalytic amount of base or Fischer esterification.[1]

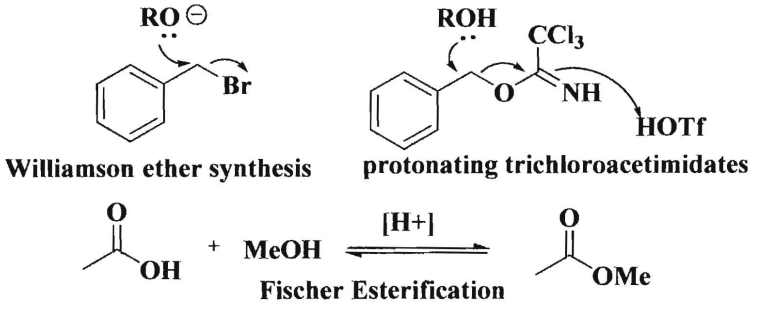


Figure 1

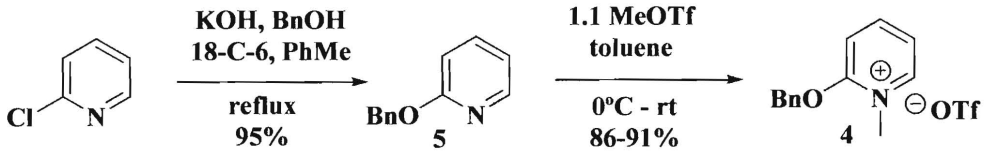
Williamson ether synthesis and use of protonated trichloroacetimidate are the most common ways of preparing benzyl ethers, but both reactions have large drawbacks. Williamson ether synthesis uses strongly basic conditions, deprotonating an alcohol and using the resulting alkoxide to attack an electrophilic benzyl synthon, such as BnBr. One problem with this strategy is the basic conditions; fragile bonds with a lot of electrophilic character will also be subject to attack by the resulting alkoxide because it is such a good nucleophile. The other problem is that the reaction relies on the nucleophilic character of the alkoxide, which decreases as the alkoxide becomes more heavily substituted, primary to secondary to tertiary. Because bulky alkoxides are more likely to form a double bond by elimination than to perform the desired S_N2 attack, β-elimination can occur on substrates with an available ß hydrogen. Milder methods, like that shown in **Scheme 3**, are abundant in literature and each addresses a unique problem associated with a specific reaction. The drawback of many of these reactions is that they take longer to complete. Scheme 3 calls for a 48 hour period, while scheme 4 is complete in under an hour.

Protonating trichloroacetimidates as a leaving group and attacking the electrophilic benzylic position features its own problems. The triflic acid (pKa ≈ -15), which is several billion times more acidic than sulfuric acid, is used to protonate the imide. Having this acid in the reaction mixture can also protonate and break many other areas with nucleophile functionality. The harshness can be toned down by changing acids, but this again adds time to the length of the reaction.

Benzyl esters can be prepared by Fischer esterification, the reaction of a catalytic amount of acid with an alcohol and a carboxylic acid, or by reacting an alcohol and acid halide or acid anhydride in the presence of a catalytic amount of base. Limitations again stem from the presence of an acid or base catalyst. General pKa of carboxylic acids is ≈ 4.5, so the pKa of the catalyst must be lower, which is relatively acidic for many biological compounds. Carboxylic acids also have restricted conditions because of the ability for Claisen condensation and enolate chemistry to occur.

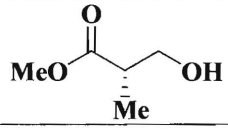
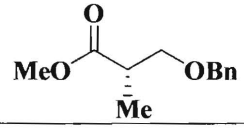
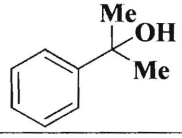
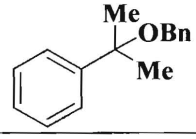
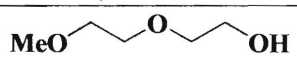
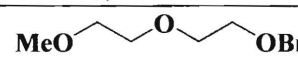
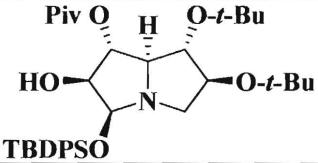
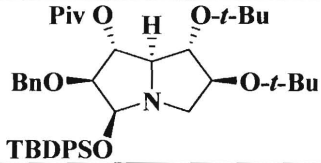
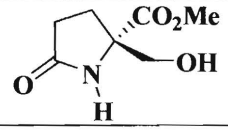
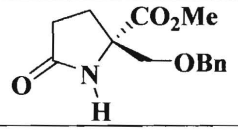
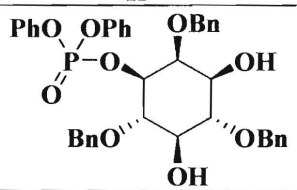
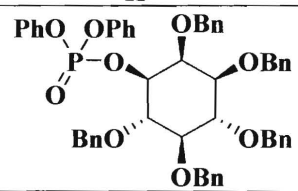
2-Benzyloxy-1-methylpyridinium Trifluoromethanesulfonate (BnOPT) **(4)** was developed as a reagents capable of producing benzyl ethers upon heating in the presence of an alcohol substrate.[10,11,12,13] BnOPT was made in two steps **(Scheme 9)**. First, benzyl alcohol was reacted with 2-chloropyridine to generate 2-benzyloxypyridine **(5)** in a S_NAr reaction. 2-

Benzyloxypyridine was then reacted with methyl triflate to generate BnOPT in an S_N2 reactio. BnOPT is a bench stable, crystalline salt easily stored at room temperature under an inert atmosphere.



Scheme 9[10]

Benzylation of alcohols occurred most efficiently with magnesium oxide present as an acid scavenger in ratios with BnOPT as shown above. The reaction can be performed in one vial under argon with heating. The table below **(Table 1)** illustrates the success of the reagent both in installing the benzyl protective group and in retaining the structure of a broad array of substrates.

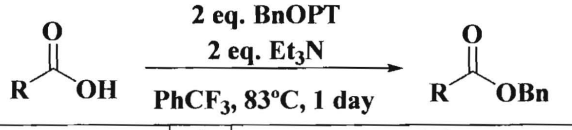
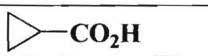
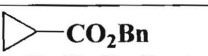
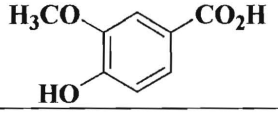
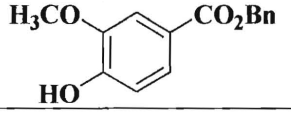
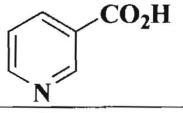
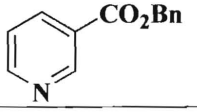
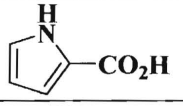
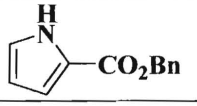
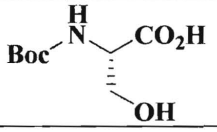
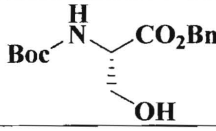
Scheme 10[13]	R–OH → (2 eq. BnOPT, 2 eq. MgO, $PhCF_3$, 83°C, 1 day) → R–O–Bn				
Entry	ROH	#	ROBn	#	Yield[a]
1[14]		**5**		**6**	85%
2[14]		7		**8**	44%
3[14]		**9**		**10**	93%[b]
4[14]		**11**		**12**	95%
5[15]		**13**		**14**	75%
6[16]		**15**		**16**	73%

[a] Yields estimated from ^{1}H NRM spectroscopy. [b] Isolated yield of pure product.

Table 1

Each of the examples in **Table 1** displays some benefit of using BnOPT over traditional methods. Entry 1 features none of the racemization that could occur under Williamson ether synthesis conditions. Entry 2 is possible, where using the hindered, tertiary alkoxide to attack a benzyl synthon would be very hard to do as the tertiary alkoxide is a poor nucleophile and is more likely to perform β-elimination. Entry 3 features no fragmentation at either of the 2 ether moieties.[13] Use of BnOPT was reported to be the only successful method for benzylation of **11** in enrty 4.[14] **4** was successful in benzylating **13** at the desire location in spite of the presence of a nucleophilic lactam moiety. Entry 6 could be benzylated by **4** with no formation of cyclic phosphates which would occur under Williamson ether synthesis conditions.[16]

Optimal conditions for benzylation of carboxylic acids using BnOPT are shown above and a table showing the success of this procedure is shown below **(Table 2)**. Of particular note, by using Et_3N as a base, it is possible to selectively benzylate a carboxylic acid over an alcohol.[17] This was discovered during a base screen undertaken during the optimization of the reaction. The base screen had to be conducted because MgO was much less effective for benzylation of carboxylic acid than for alcohols. Indeed, using no base was more effective than MgO.[17] A dibenzyl ether byproduct also formed during the reaction.[17] Bases were tested both for efficiency and minimization of byproduct, where K_2CO_3 was the most efficient base but Et_3N gave no byproduct.[18] This dual role of weak base to activate the carboxylic acid and phenylcarbenium scavenger is the reason Et_3N was used over K_2CO_3.[17]

Scheme 11[17]					
Entry	ROOH	#	ROOBn	#	Yield
1		17		18	98%
2		19		20	91%[a]
3		21		22	81%[b]
4		23		24	86%
5		25		26	91%
					>99%

Again, each of the entries in **Table 2** (above) displays a result different from what would be expect using more common methods. The cyclopropane ring remains unbroken in entry 1, which is significant because of the amount of strain present in this highly reactive structure. Entry 2 demonstrates that, by using Et_3N, it is possible to selectively benzylate carboxylic acids over alcohols. Entries 3 and 4 shows benzylation of the carboxylic acid with some electron density drawn away and no benzylation occurring at the nitrogen of the ring. Entry 5 shows benzylation of a carboxylic acid over an alcohol, no racemization, no benzylation of the nitrogen, and no loss of the Boc group, which would be removed under strongly acidic conditions found in some common methods. Entry 6 shows a quantitative yield with no disruption of the many ether moieties or racemization. Strong base would cause heavy fragmentation in **27**.[17]

For all the utility and efficiency displayed above, BnOPT is not without its own unique set of problems. The salt is insoluble in most organic solvent, so the reaction only occurs at the surface where the solvent containing the substrate interacts with solid BnOPT. The reaction also proceeds best at roughly 80°C, when the salt melts and mixing can occur slightly more efficiently.[12] This temperature limits possible substrate to compound that can withstand the temperature. Reaction efficiency is also limited from tertiary alcohols and phenols. That being said, using BnOPT made it possible to benzylate some compounds that previously lacked methods.

1.2 Mechanism

Figure 2 (below) shows the extreme boarders of reaction pathways that the benzylation reaction could occur along. In an S_N1 reaction, **4** would break apart at the weak bond (shown in red) between the benzyl cation and the oxygen at the 2 position in the pyridine ring. The benzyl cation would then be attacked by alcohol, forming the benzyl ether. 1-methyl-2-pyridone **(29)** would be generated as a byproduct as electrons push around the ring to neutralize the charge on nitrogen. The S_N2 pathway would occur with the alcohol attacking the electrophilic benzylic position first and ejecting **29** second. In the S_N2 pathway, the benzylic position is made progressively more reactive as temperature is increased, whereas decomposition is the thermally dependant portion in S_N1. The true reaction probably lies somewhere between S_N1 and S_N2 on a linear spectrum, with more S_N1 character than S_N2.[12]

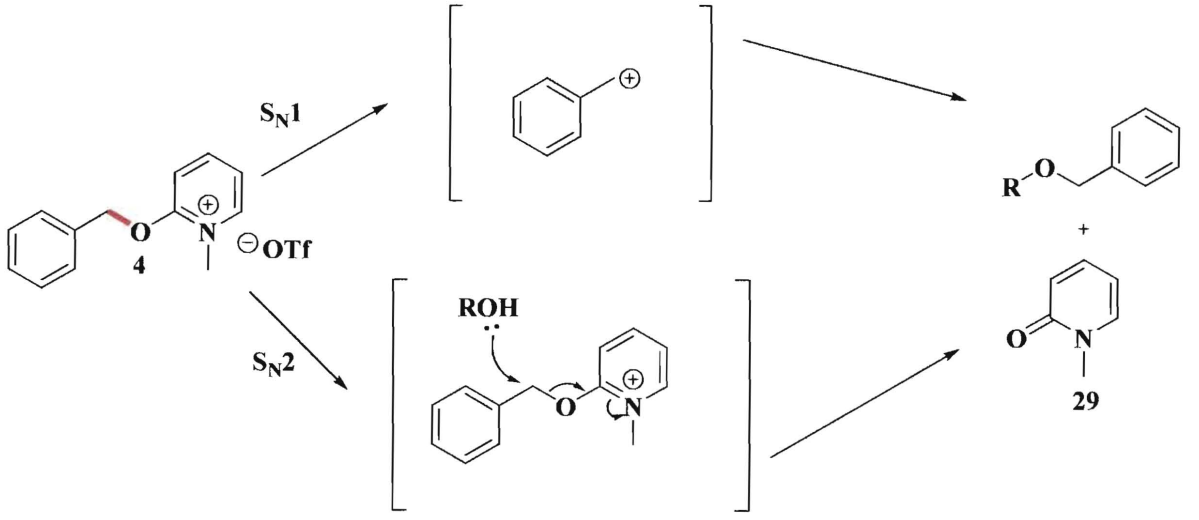
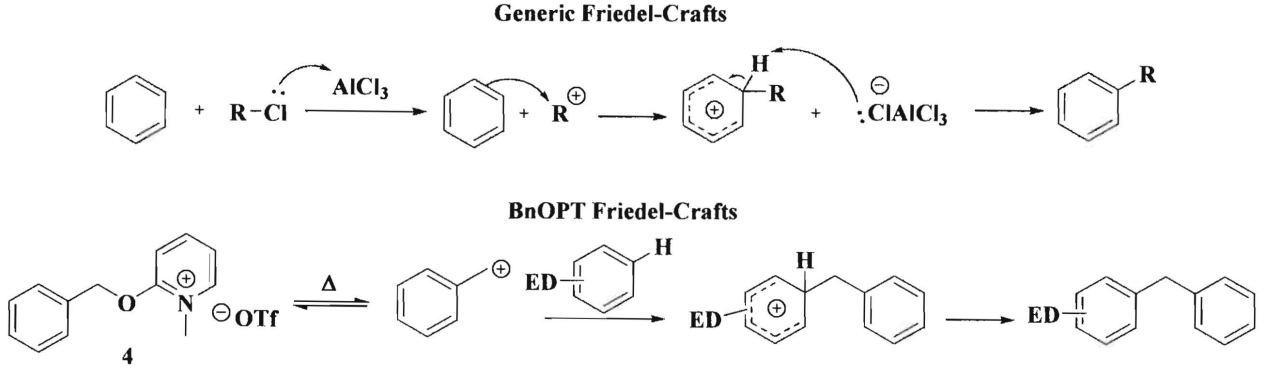


Figure 2[12]

1.2.1 Supporting evidence

Several observations of phenomena support the mechanism above. The supporting evidence is described in sections below.

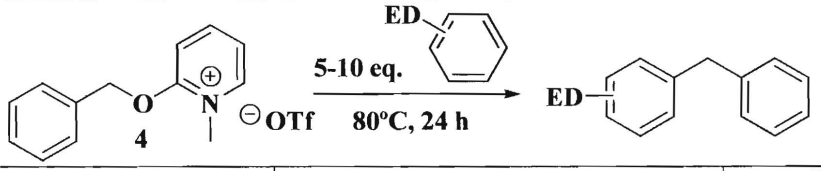
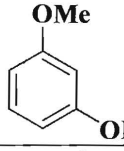
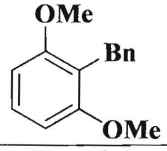
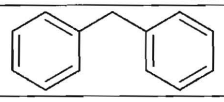
4 has been shown to be a successful reagent for Friedel-Crafts alkylations **(Scheme 12)**.[18]



Scheme 12[18]

4 undergoes thermolysis producing a benzyl cation and 1-methyl-2-pyridone.[18] An aryl species attached to an electron donor can then attack the strongly electrophilic benzyl cation and form a

new carbon-carbon bond. **29** can then deprotonate the aryl species. This shows the same general behavior as the aluminum chloride complex used to generate a cation in this general Friedels Craft scheme **(Scheme 12)**. While Friedel-Crafts alkylation typically features strong Lewis acids to generate the cation, this reaction is acid free. The fact that Friedel-Crafts can occur using this method shows the strong S_N1 character of the mechanism.[18] For Friedel-Crafts to occur, the strength of the bond highlighted in mechanism 1 must be negligible so the cationic character of the benzylic position is not stabilized. The success of this reaction is displayed in **Table 3**.

Scheme 14[18]			
Entry	Arene	Product	Yield[a] (ratio)[b]
1			100 (12:88)
2			43

[a] Yields refer to isolated product judged to be >95% by ^{1}H NMR spectroscopy. All comounds provided characterization data in accord with the literature reports. [b] Regioisomer ratios estimated by ^{1}H NMR.

Table 3[18]

The entries in **Table 3** show the results of using **4** as a reagent for performing Firedel-Crafts alkylation. Entry 1 is a typical example with donor groups present at both ortho positions. Entry 2 has alkyl donor groups at both ortho and the para position. Entry 3 features a bromo group in the ortho position, which is slightly deactivating, but the reaction still proceeds fairly well. Entry 4 shows that the reaction can proceed without any activation, using only benzene.[18]

Another piece of evidence for the predominantly S_N1 behavior of the mechanism is the difference in reactivity of generating a methyl cation verses a *t*-butyl cation from analogous substrates **(30 and 31)**.

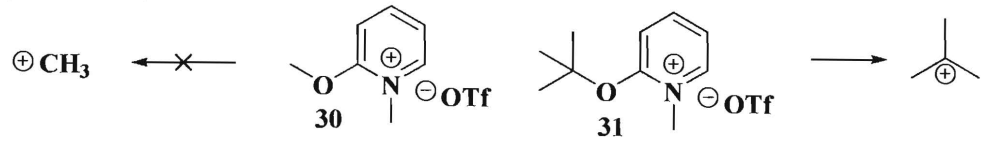


Figure 3

Other members of the research group have explored both reagents to gauge the utility of the reagents in protection chemistry. Observed results have shown that methyl groups cannot be transferred through this method ,even when stirred in the presence of simple alcohols at 83°C for 24 hours.[19] *t*-Butyl groups can be transferred at room temperature or below in less than 3 hours **(Table 4)**.[20] This evidence supports S_N1 because the cation intermediate would be extremely unstable for a methyl group, but relatively stable for a *t*-butyl group.

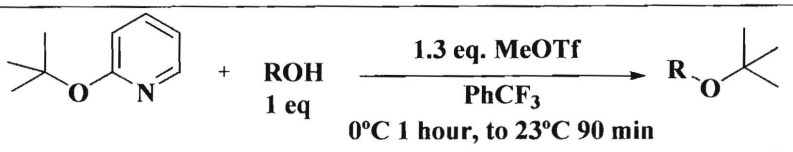
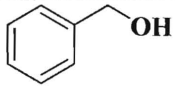
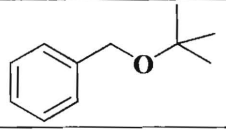
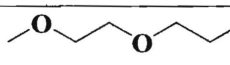
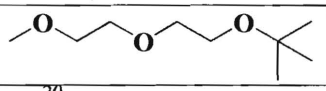
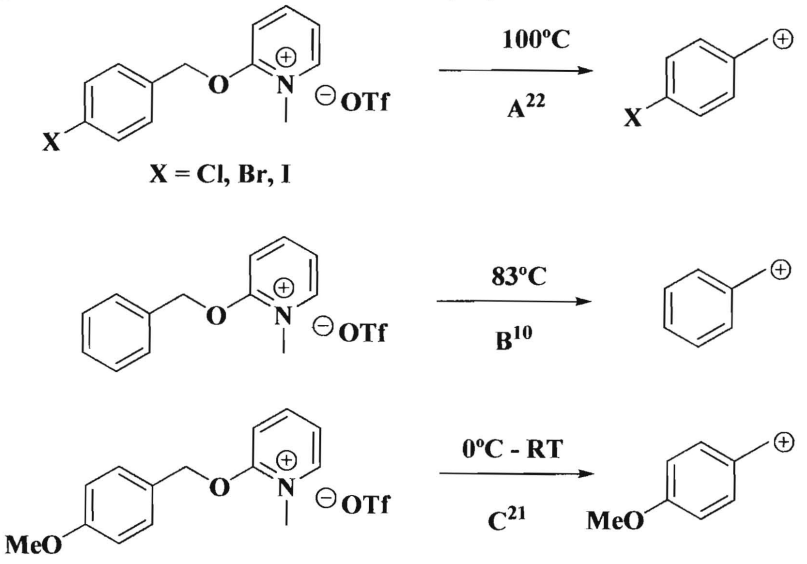
Scheme 15[20]			
Rnx	ROH	RO-*t*Bu	Yield
1			90%
2			92%

Table 4[20]

Adding an electron donating group to the benzyl ring **(Reaction A of Scheme 16)**[21] pushes electron density into the ring and helps stabilize the positive the charge of the benzyl cation. This stabilization enables decomposition to occur at a lower temperature, ≈ 0°C.[21] Alternatively, adding an electron withdrawing group, such as a halogen, destabilizes the cation and raises the reaction temperature **(Reaction C of Scheme 16)**.[22] In the case of halogens, the temperature increases from 80°C to 100°C. The magnitude of the change created by adding and electron donating or withdrawing group differentiates between an S_N2 and S_N1 mechanism according to the Hammett equation; the larger the difference between electron donating and electron withdrawing groups, the more cation character is displayed.



Scheme 16

When strong electron withdrawing groups are placed in meta positions on the pyridine ring of **4**, decomposition to give the benzyl cation occurred at a reduced temperature, ≈ 60°C.[19] While this has benefits for the utility of the reaction because it becomes possible to use more sensitive substrates as the reaction temperature lowers, the electron withdrawing groups make **5** a poorer nucleophile and it becomes harder to generate **4** from reacting **5** with MeOTf **(Scheme 9)**.

1.3 Summary

The literature and discussion presented in chapter 1 has demonstrated the utility of **4** as a reagent for mix-and-heat benzylation of oxygen nucleophiles in mildly basic conditions. Conditions for benzylation using **4** are comparatively mild because the benzyl cation is produced through thermolysis. Mechanistic extremes for the reaction have been defined and experimental evidence has been presented to support the supposed tendency of the mechanism within those extremes. **4** has been used as a benzylation reagent successfully where no other methodology would work. Because **4** decomposes by thermolysis, it should be possible to generate other carbocations the same way. Experimentation has already shown that methyl cations cannot be transferred through this method and that *t*-butyl cation can be transferred extremely well. The allyl group is another common alkyl protection group used for oxygen nucleophiles. It should be possible to transfer an allylic cation through an analogous reagent **(Figure 4)**.

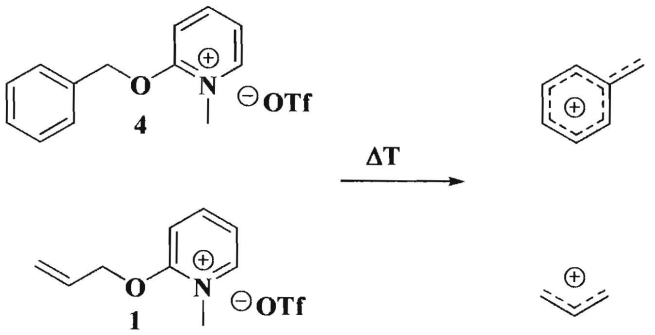


Figure 4

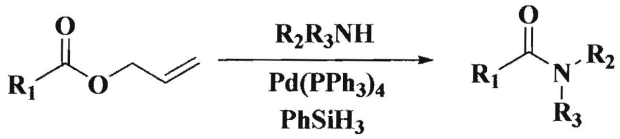
Chapter 2: 2-Allyloxy-1-methlpyridinium Trifluoromethanesulfonate and Derivatives

2.1 Theory

The allyl group has significant utility as a protective groups across a wide range of substrates.[1] Allylic cations are more stable than methyl cations, so it may be possible to install an allyl cation with a reagent similar to **4**. However, allyl cations are more unstable than benzyl cations and installing allyl groups as protection groups can require harsh methods.

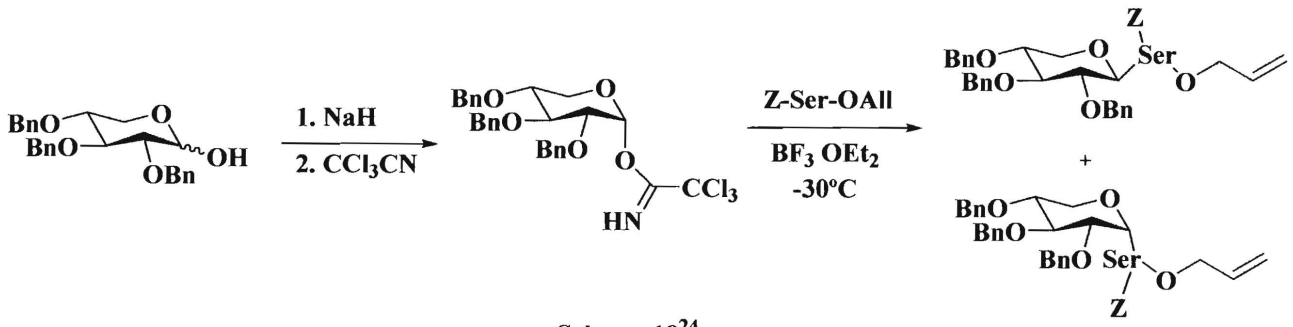
2.2 Allyl Esters and Ethers

Allyl esters and ethers are both particularly important as protective groups in biological synthesis of carboxamide drug precursors **(Scheme 17)**[1,23] and glycopeptides **(Scheme 18)**[1,24] because of the stability exhibited under moderately acid or basic conditions and because of the potential for selective removal of the protection group under mild conditions.[25]



Scheme 17[23]

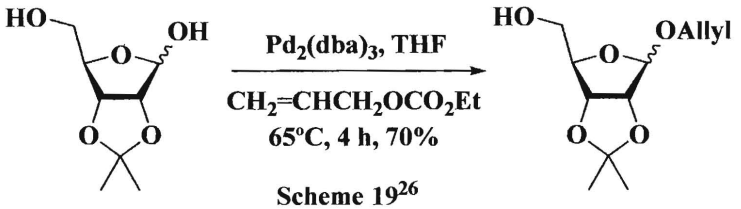
In **Scheme 17**, the allyl ester protection group is converted directly to a dialkyl amide through use of Pd (0) catalyst and phenylsilane. The reaction can be carried out in one step at room temperature with primary and secondary amines giving high yields with high purity.[23] This shows the value of the allyl protection group as a synthon.



Scheme 18[24]

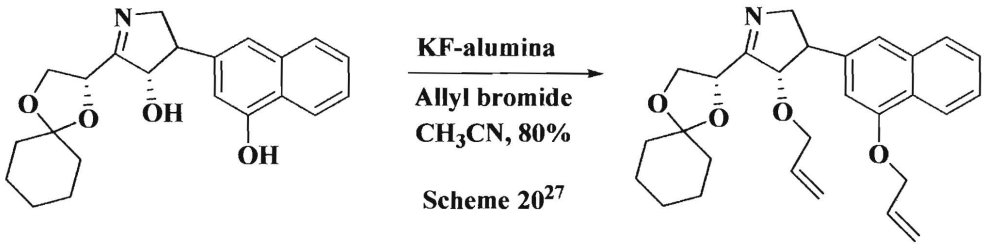
In **Scheme 18**, an allyl group is used to mask a hydroxyl group in Z-serine before reacting serine with the trichloroimidate to generate the two serine glycosides shown.[24] The two isomers could then be separated by chromatographic methods.[24] This method also worked for threonine.[24]

Allyl ethers can be synthesized in one step under neutral conditions using carbonic acid allyl ethyl ester and a catalytic amount of palladium **(Scheme 19)**.[26]



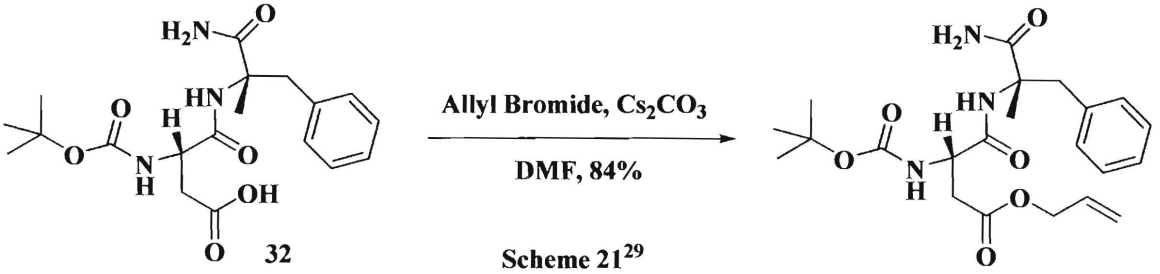
Scheme 19[26]

The reaction occurs preferentially at the anomeric hydroxyl,[26] making this particularly useful in modifying monomers of carbohydrates before polymerization. The method is also effective for primary and secondary alcohols.[26] **Scheme 20** shows protection of a naphthol group and isoxazoline group by allyl bromide and potassium fluoride impregnated alumina.[27] This method was developed to prevent the Beckmann fragmentation of the isoxazoline in typical alkylation conditions using strongly basic metals.[28]



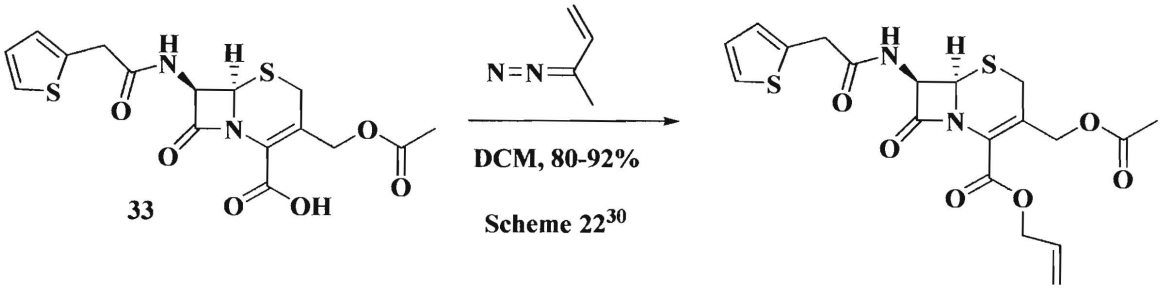
Scheme 20[27]

Alcohols can also be masked with allyl esters. An allyl ester can be synthesized from an alcohol with an allyl synthon and carbonate. **Scheme 21** displays this method being used on Boc-Asp-Phe-NH_2 **(32)**.[29]



Scheme 21[29]

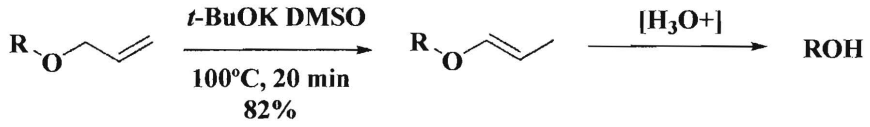
Allyl esters can also be generated from carboxylic acids in mild conditions using vinyldiazomethane.[30] The method is scene here used on Cefalotin **(33)**, a cephalosporin **(Scheme 22)**.[30]



Scheme 22[30]

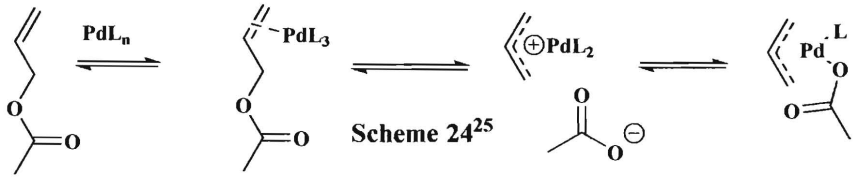
Cephalosporins are a class of antibiotic. The protective function carried out here by the allyl group is valuable to making new varieties of antibiotic with the cephalosporin frame. Caution should be used when attempting this method as alkyldiazo compounds are explosive. All of these methods address unique problem associated with the reaction they were used in. Allyl esters and ethers can also be prepared using the general methods discussed in chapter 1.

Allyl ethers are typically cleaved through S_N2' isomerization, where a strong base attacks the terminal end of the allyl protective group, followed by mild acid catalyzed hydrolysis **(Scheme 23)**.[31]



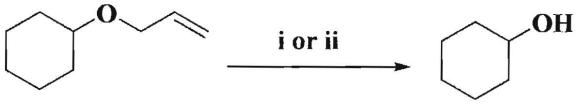
Scheme 23[31]

Isomerization can occur through the use of transition metal catalyst instead of strong base. This allows for neutral cleavage conditions and adds preserved the medicinal chemistry utility of the protective group.[32]Palladium can retro-insert into allyl-carbonyl bond in an allyl ester and then recombine a different ligand with the carboxylate anion to form a new ester in a process called transesterification **(Scheme 24)**.[25]



Scheme 24[25]

This reaction is very mild, requiring no acid, base, or heat. The cleavage is also highly selective, poorly cleaving allyl ethers and allyl amine species.[25] The only requirement is that the ester formed be more stable than the allyl ester, or that the allyl group be a better ligand than the pieces it is displacing. Samarium iodide is another good complexing reagent for the removal of allyl groups.[33] This reaction uses bases of moderate strength, but progresses very quickly. Isopropyl amine is quite basic (pKa ≈ 10.6), but give quantitative yields in one minute **(Scheme 25)**.[33]



i = $SmI_2/H_2O/Et_3N$, rt, 2 h, >99%
ii = $SmI_2/H_2O/i$-$PrNH_2$, rt, 1 min, >99%

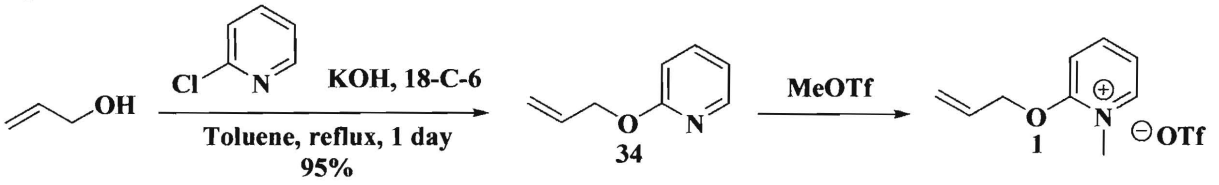
Scheme 25[33]

The limitations of many of these methods are similar to the limitations discussed in chapter 1, mostly that the method requires that the substrate is able to withstand the conditions the reaction calls for. It is worth noting that reactions with allylic cation character in an intermediate will have a higher transition energy than the benzyl intermediate, but less problems with steric hindrance.

2.3 Allyloxypyridinium Salts and Derivatives

Because allyl and benzyl structures have similar properties, it should be possible to install each as a protective group using similar methods. Allyl cations are less stable than benzyl cations, but are also less sterically hindered. There is also the possibility for S_N2' chemistry to occur at the terminal carbon when changing from the benzyl group to the allyl group.

2-allyloxypyridine **(34)** can be prepared by reaction 2-chlropyridine with allyl alcohol in the presence of potassium hydroxide and 18-crown-6 ether **(Scheme 26)**.[34]

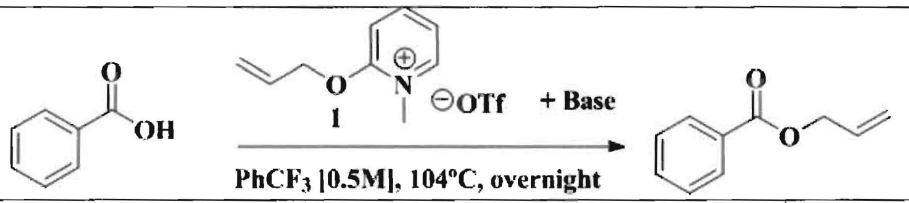


Scheme 26

Unlike BnOPt, **1** is not a crystalline salt. **1** is amorphous and adsorptive, so **1** is generated *in situ* for each reaction to avoid adding impurities to reactions. [34]

My research began with testing the effectiveness of **1** as an allylating agent against hexanoic acid and benzoic acid. The reaction was then being done with Et_3N as a base because it was the best base for carboxylic acids in the benzyl methodology.[17] Here however, Et_3N is believed to be outcompeting the carboxylates as nucleophiles. Because of this potential for competition, another base screen investigation was begun as described above. The results of the investigation are shown below in **Table 5**. K_2CO_3 was the best base out of those tested with DBU also being noted for not allowing any byproduct to form. DBU does not sufficiently activate the carboxylic acid to prevent methyl benzoate from forming, so K_2CO_3 is still more highly recommended.

Scheme 27



Base	Products (%)				Total Recovery?
	Allyl Benzoate	Methyl Benzoate	Byproduct	Benzoic Acid	
None	67	11	22	~0	Yes
K_2CO_3	85	~0	10	5	Yes
$NaHCO_3$	50	~0	50	~0	No ~77%
MgO	27	3	72	~0	Yes
Et_3N	63	6	23	2	Yes
Lutidine	13	~0	47	40	Yes
DBU	80	20	~0	~0	Yes
DIPEA	53	23	23	~0	Yes

This table gives ratios of product formed based on integration of ^1H NMR of an isolated, crude product.

Table 5

Methyl ester was being created along with the desired allyl ester. Methyl ester could be created from two sources in reactions generating **1** *in situ* **(Figure 5)**, the methyl attached to the nitrogen of the pyridine ring or directly from methyl triflate.

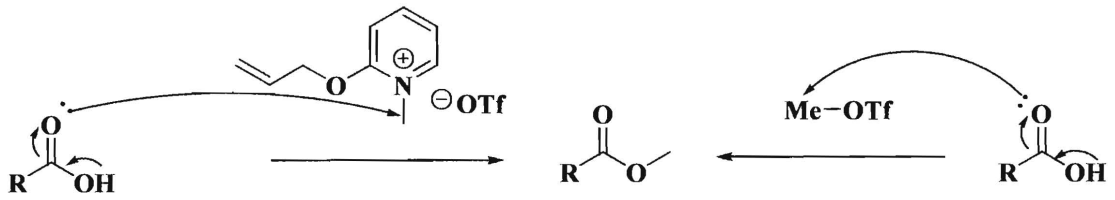


Figure 5

Of the two, methyl triflate is the more reactive, but both are comparatively reactive to the allyl site if **1** does not decompose. Not only is methyl triflate a highly reactive source of a methyl cation, it is also extremely toxic and carcinogenic. Finding a way to handle methyl triflate less would increase the appeal of this reaction and remove one possible route of generating unwanted methyl ester.

Because decomposition of **1** is reliant on temperature, the logical step would be to crank up the heat. The reaction was already being run at 104°C, roughly the boiling temperature of the $PhCF_3$, so another screening to find a replacement solvent had to take place. Xylenes and chlorobenzene were both tested as replacement solvents for their higher boiling points. The results are shown below in **Table 5**. The xylenes mixture was unsuccessful as a replacement solvent because the reagents dissolved even less in xylenes than in $PhCF_3$. Chlorobenzene was a success and showed better decomposition of **1**. During the solvent trials, it was also noted that a reduction in excess molar ratios of **1** and base would minimize the amount of byproduct from **Table 4** that formed. A clear structure of this byproduct was never obtained and the byproduct would blacken when exposed to air. Based on these two observations, it is hypothesized that remaining allyl cation would polymerize into a branching chain with the aid of remaining carbonate.

Solvent	Temp (°C)	Improvement (Y/N)[1]
$PhCF_3$	100	Orig.
Xylenes	100	No
Xylenes	130	Yes
Chlorobenzene	100	No
Chlorobenzene	130	Yes
Chlorobenzene	125	Yes[2]

[1] Improvement meant either an increase in crude recovery of allyl ester without an increase in impurity, or a decrease in methyl ester and byproduct formation without a decrease in overall yield. [2] This result was more successful than the previous trial after changing ratios of reagents **(Table 6)**.

Table 5

Reagent	Ratio 1	Ratio 2	Ratio 3
Benzoic Acid	1	1	1
34	2	1.2	1.2
MeOTf	2.4	1.3	1.2
Base	2	1.2	1
Solvent	0.5 M	0.5 M	0.5 M

Table 6

1 has proven capable of transferring an allyl group, but fall short of the initial goal in two categories: mild conditions and reliability. Decomposition of **1** was approaching 100% at 135°C, but the products of the reaction also has a tendency to decompose at this high temperature. The reaction was 55°C hotter than the benzylation reaction and still not at completion. The reaction was also unreliable. There was a window of ±10% yield to consecutive reactions based on the extent of decomposition of the salt and the efficiency of mixing. The source of allyl cation was changed from **1** to 2-allyloxy-1,4-dimethylquinolinium trifluoromethanesulfonate **(AOdMQT) (2)** to deal with these problems. **2** can be prepared from 2-chloro-4-methylquinoline **(35)** and allyl alcohol using a procedure analogous to that shown in **Scheme 26.**

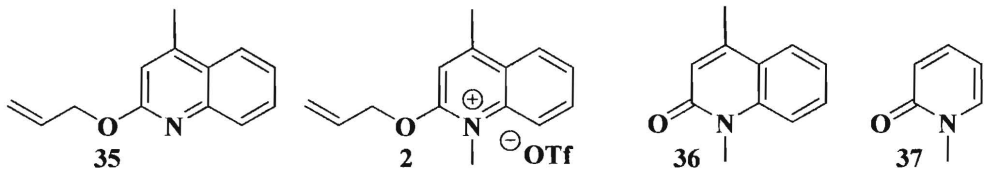


Figure 6

2 is a bench stable, crystalline salt that can be stored under inert gas and added as needed to reactions. Changing from **1** to **2** lessens the need to handle methyl triflate and removes one pathways for the generation of methyl ester. The extra ring in **2** adds enough stability to the structure to make **2** a solid crystal at room temperature. The ring may also increase solubility of the triflate salt in organic solvents. The added stability also allows the reaction to proceed faster and at a lower temperature of 104°C. The change removes two large problems, but adds one small inconvenience. 1,4-dimethyl-2-quinolinone **(36)** is not water soluble and must be separated from the desired product by flash column chromatography, whereas 1-methyl-2-pyridone **(37)** was water soluble. By comparing results from crude ^{1}H NMR spectroscopy, it was found that the change in reagent increased repeatability and efficiency of reaction.

At this point, a colleague continued to work on carboxylic acids as I moved to beginning the work on alcohols. Another base screen like those described above found that K_2CO_3 was again the best base to use with **2**. The screen was ran again because BnOPT could select for carboxylic acid or alcohol depending on the base used.[18] TLC and ^{1}H NMR both showed complete consumption of the salt, so a solvent screen for higher temperatures was deemed unnecessary. After implementing changes discovered from results of kinetics experiments run on carboxylic acids, this method will be ready to test against a broad array of alcohols to test utility and develop further.

This discussion has shown that **2** is an effective reagent for synthesizing allyl esters under mild conditions for use as protective groups when used as discussed above. The method is mild, efficient, and reliable, fulfilling three of the goals in the installation step of protection group

theory. Other methodology and literature has been referenced and discussed detailing the merit of allyl protection groups in the transformation and cleavage steps of protection chemistry, which this method will not interfere with. The hypothesis that **1** and **2** would be effective reagents for allylation of oxygen nucleophiles has been proven true.

Appendix A: Experimental Procedures

General Notes

All glass was dried overnight in an oven at and cooled in a desiccator. All reaction were set up with positive argon pressure. Reflux reactions were allowed to reflux with open atmosphere.

Preparation of 2-allyloxypyridine

7.0 g of 2-chloropyridine was reacted with 5.0 mL of allyl alcohol in 60 mL of toluene in a 250 mL round bottom 3-neck flask with a reflux column at 83°C overnight. The reaction is driven by 14.5 g of freshly ground KOH pellets with 0.163 g of 18-C-6 ether to help solubility of KOH. Completeness of the reaction can be judged by using thin layer chromatography (TLC). With a 49:1 hexane: ethyl acetate eluent and an I_2 chamber for staining, the allyl group on unconsumed alcohol and on **34** can be visually compared. Allyl alcohol had an $R_f \approx 0$, **34** has an $R_f \approx 0.6$, and 2-chloropyridine had an $R_f \approx 0.3$. The mixture can be isolated by a normal separate and wash organic workup using brine and ethyl acetate. After transferring the solubilized reaction mixture to a separatory funnel with distilled water and ethyl acetate, the mixture was separated into aqueous and organic soluble layers. The organic layers were washed with three measures of concentrated brine solution, which was then added to the aqueous layer. Three measures of ethyl acetate were then used to extract any remaining organic material from the aqueous layer and added to the organic layer. The organic layer was dried over Na_2SO_4, vacuum filtered, and rotovapped to dryness for a crude yield 8.203 g (98.3%). The crude mixture is purified by purification by Kugelrohr distillation, giving 7.932 g of pure product (95% yield). The purity of **34** can then be tested with ^{1}H NMR spectroscopy. Methyl triflate can then be added to **34** to generate **1**, best done at 0°C to minimize undesirable side reactions.

Initial Base Screen of AOPT

Benzoic acid (80 mg/ 0.6551 mmol, 1 eq.) was reacted with **34** (176.5 µL, 1.310 mmol, 2 eq.), MeOTf (172.2 µL, 1.572 mmol, 2.4 eq.), and desired base (2 eq.)in 2.5 mL of dry trifluorotoluene in a 5 mL reaction vial or a 5 mL round bottom flask at 104°C overnight. The reaction was separated after completion using dichloromethane and brine. Separation procedure same as above, with DCm replacing ethyl acetate. Completion could be tested with TLC in the same eluent as **34**, where allyl benzoate and **34** had an $R_f \approx 0.3$, nonpolar particulate like grease had an $R_f \approx 1$, unconsumed **1** and benzoic acid had an $R_f \approx 0$. Unconsumed benzoic acid did not appear in a $KMnO_4$ stain, but did appear under a UV lamp, as did allyl benzoate.

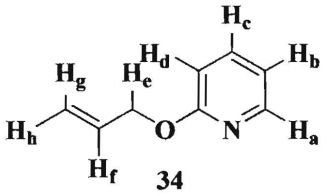
Solvent Screen of AOPT

The same reaction scheme and setup were used as discussed in the base screen section (above). This time temperature and solvent were varied instead of base, which was K_2CO_3 for all trials. Solvents were tested both at 104°C and at reflux. Improvement was based on a qualitative comparison of ^{1}H NMR spectra of crude reaction mixture isolated after workup in a separatory funnel. Ratio of reagents was also varied and ratio 2 from **Table 6** eventually replaced ratio 1 for lack of byproduct generated.

Base Screen of AOdMQT

The base screen of **2** proceeded as outline for the base screen of **1**, with the exception that the lower molar ratios of reagents discussed in the solvent optimization section were used in place of the initial molar ratios **(Table 6, ratio 3 was used in place of ratio 1)** and the amount of benzyl alcohol used each trial was dropped to 40 mg (.328 mmol). No MeOTf was used, as **2** was a preformed salt. Separation and purification procedures are the same as the base screen for compound **1**.

Appendix B: Spectral Data

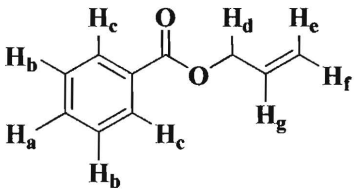


34

2-allyloxypyridine

Prepared according to procedure listed under **preparation of 2-allyloxypyridine** in Appendix A.

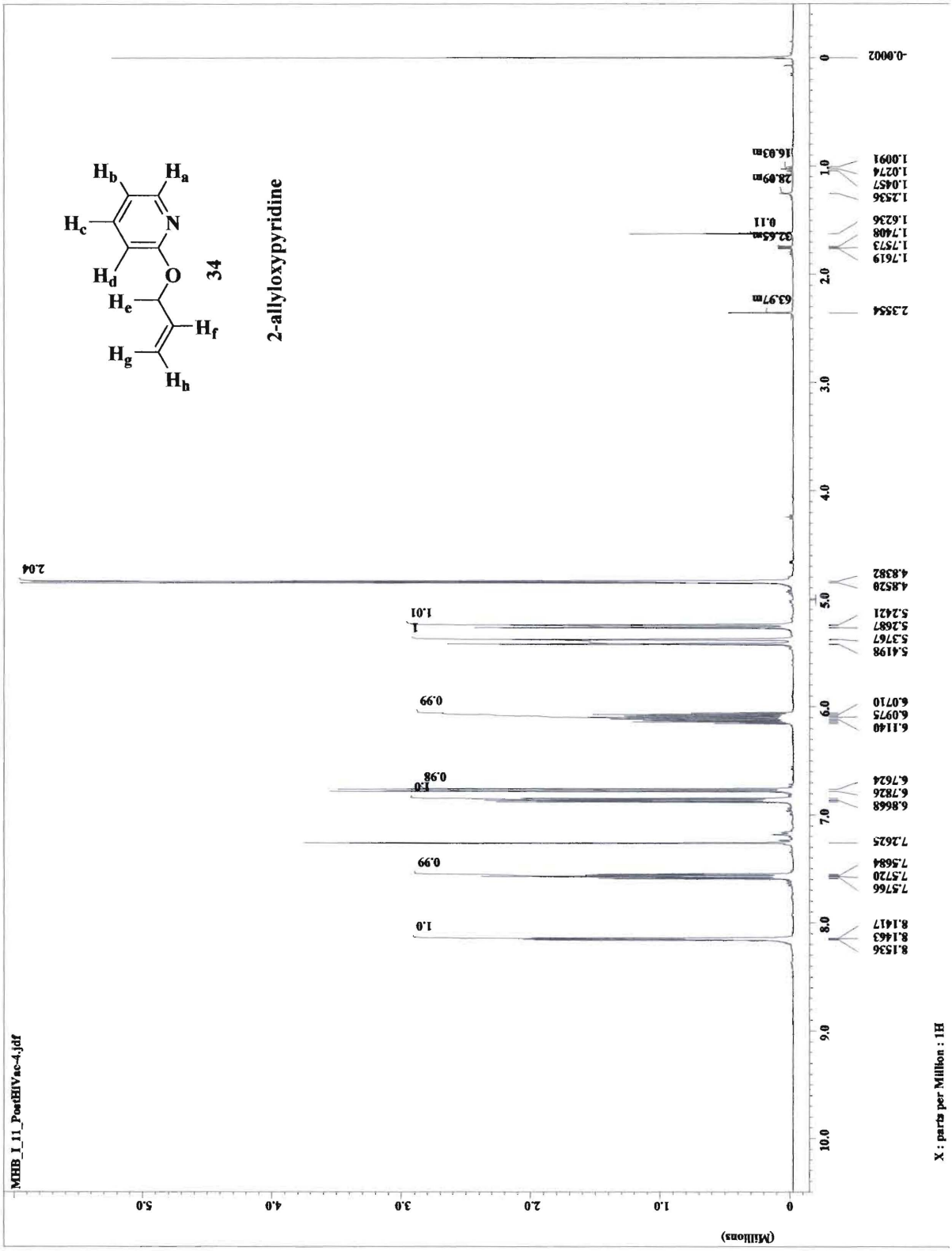
2-allyloxypyridine (34) (7.9319 g of clear, colorless oil, 95% yield) (~ 97% purity); ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 4.85 (d, J = 5.52 Hz, 2 H_e), 5.26 (dd, J = 10.64 Hz, 1.08 Hz, 1 H_h), 5.40 (dd, J = 17.24 Hz, 1.48 Hz, 1 H_g), 6.11 (m, 1 H_f), 6.77 (d, J = 8.08 Hz, 1 H_d), 6.8643 (t, J = 6.04 Hz, 1 H_b), 7.57 (dt, J = 8.44 Hz, 6.96 Hz, 1.76 Hz, 1 H_c), 8.15 (dd, J = 4.76 Hz, 2.02 Hz, 1 H_a). Peaks of lower ppm on spectrum are persistent impurities, ~3.5% of signal.

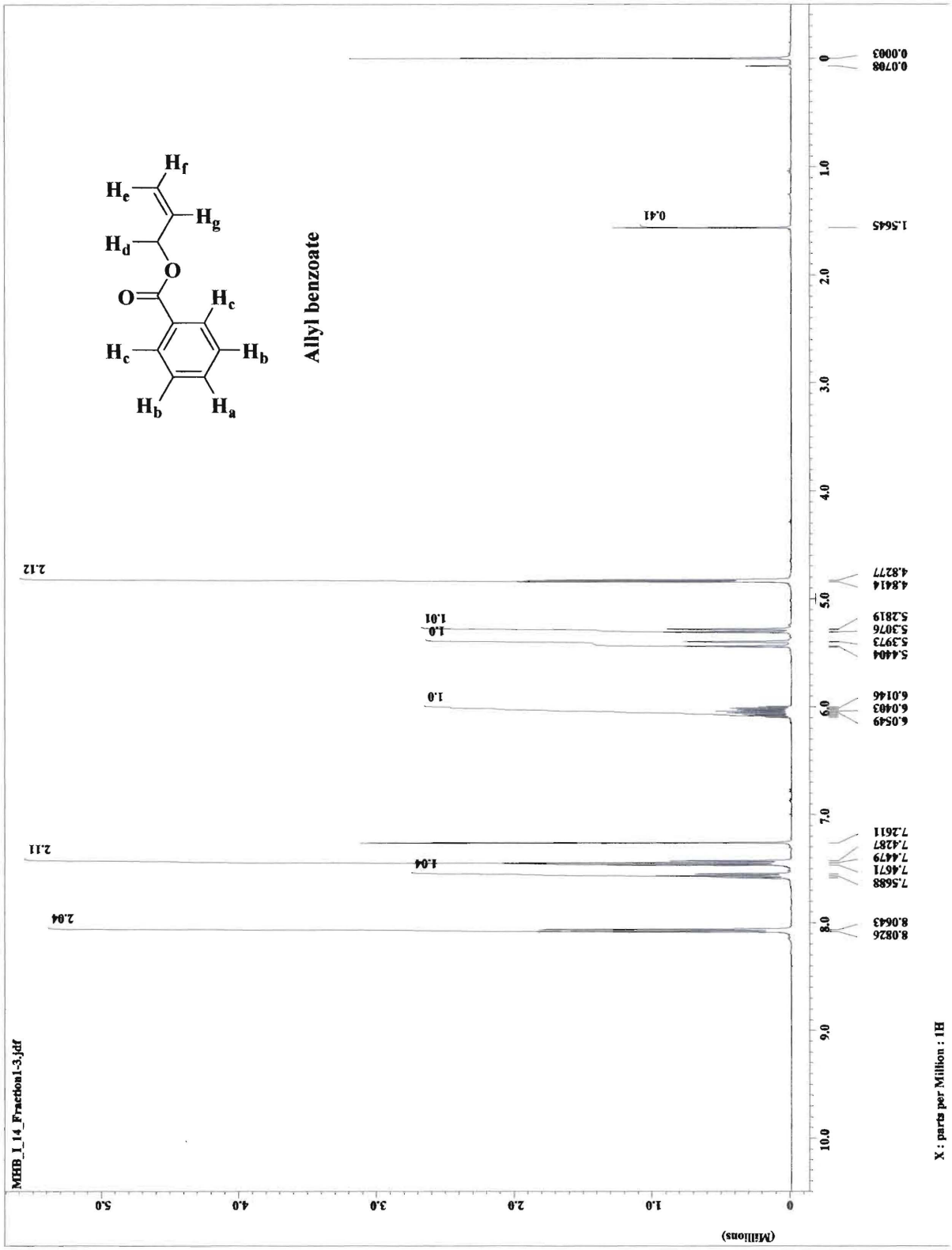


Allyl benzoate

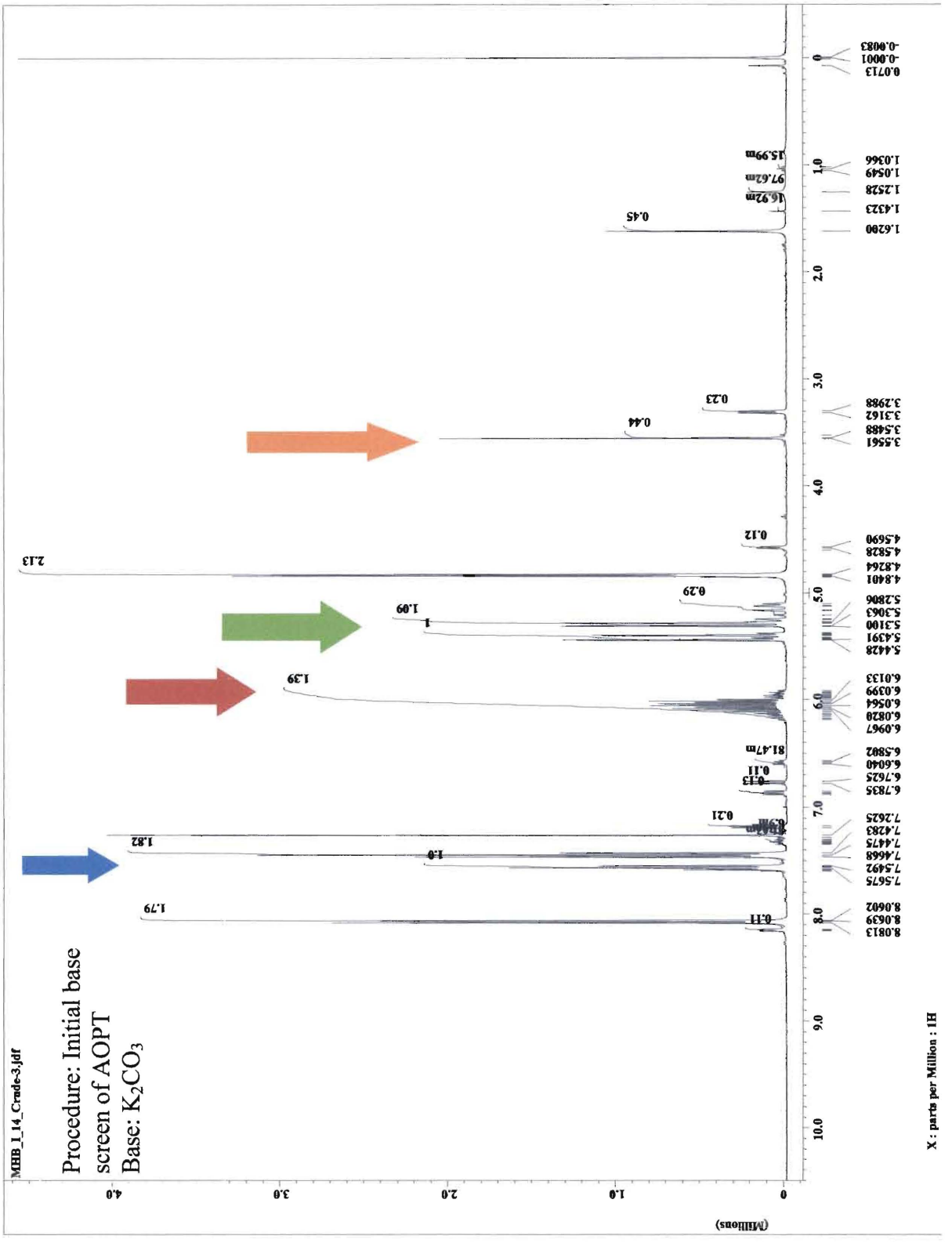
Product of all testing/screening procedures in Appendix A.

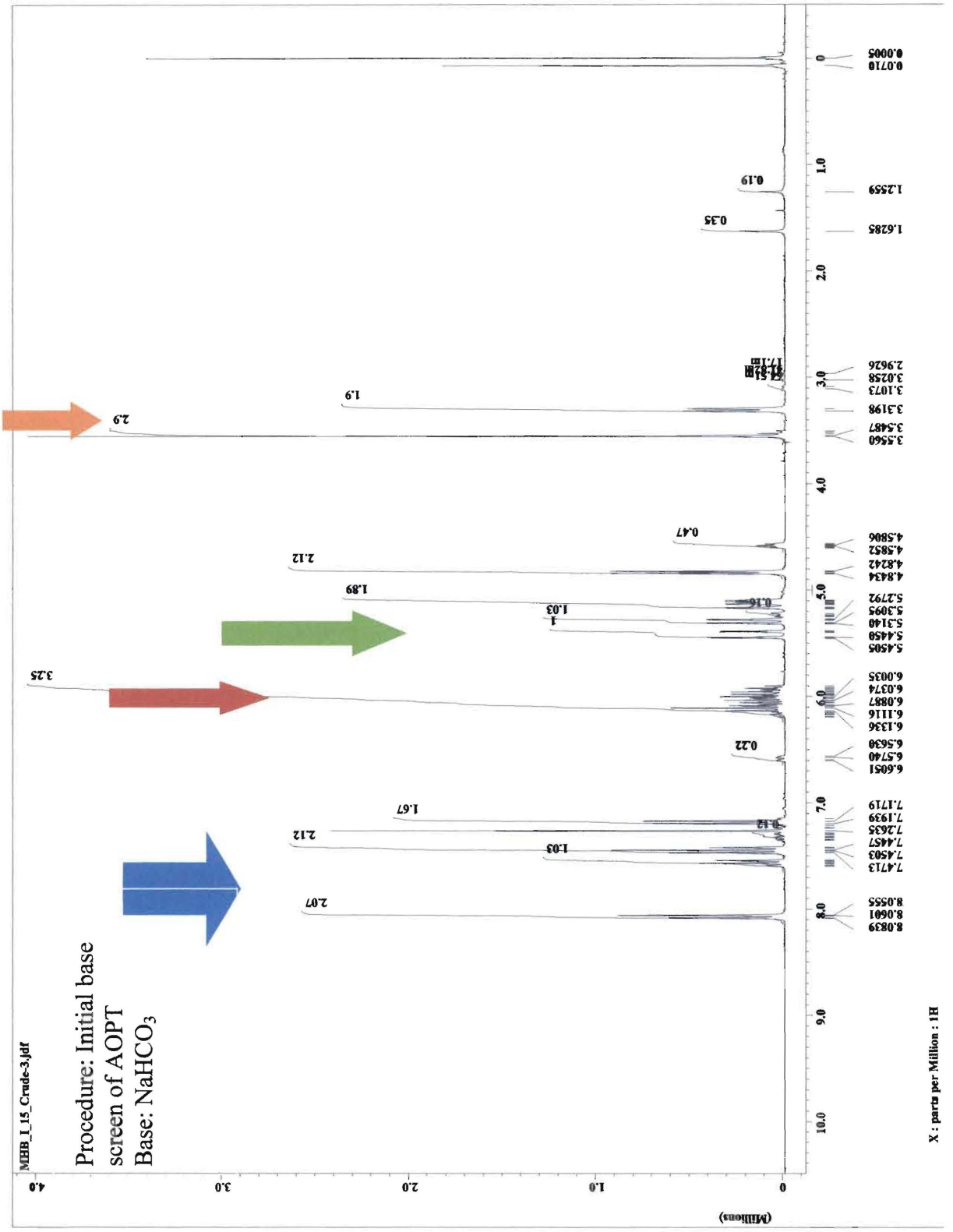
Allyl benzoate. (white crystal); ^{1}H NMr ($CDCl_3$, 400 MHz) δ: 4.83 (d, J = 5.48 Hz, 2 H_d), 5.30 (dd, J = 10.46 Hz, 1.3 Hz, 1 H_e), 5.42 (dd, J = 17.24 Hz, 1.48 Hz, 1 H_f), 6.05 (m, 1 H_g), 7.45 (t, J = 7.68 Hz, 2 H_b), 7.57 (t, J = 7.32 Hz, 1 H_a), 8.07 (d, J = 7.32 Hz, 1 H_c). Singlet present downfield is from water contamination in deuterated chloroform solvent.

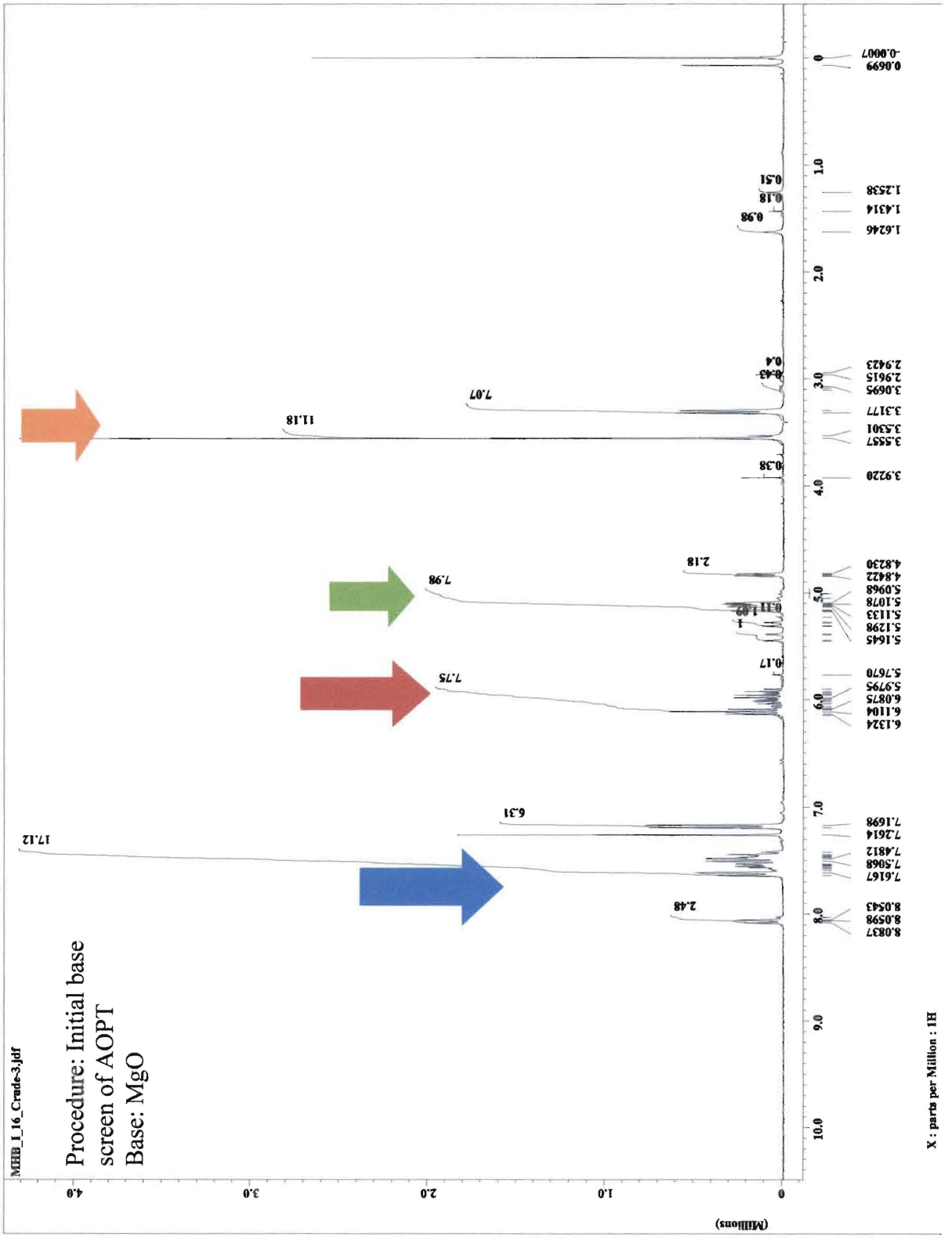

2-allyloxypyridine
34
MHB_I_11_PostHiVac-4.jdf
X : parts per Million : 1H
(Millions)

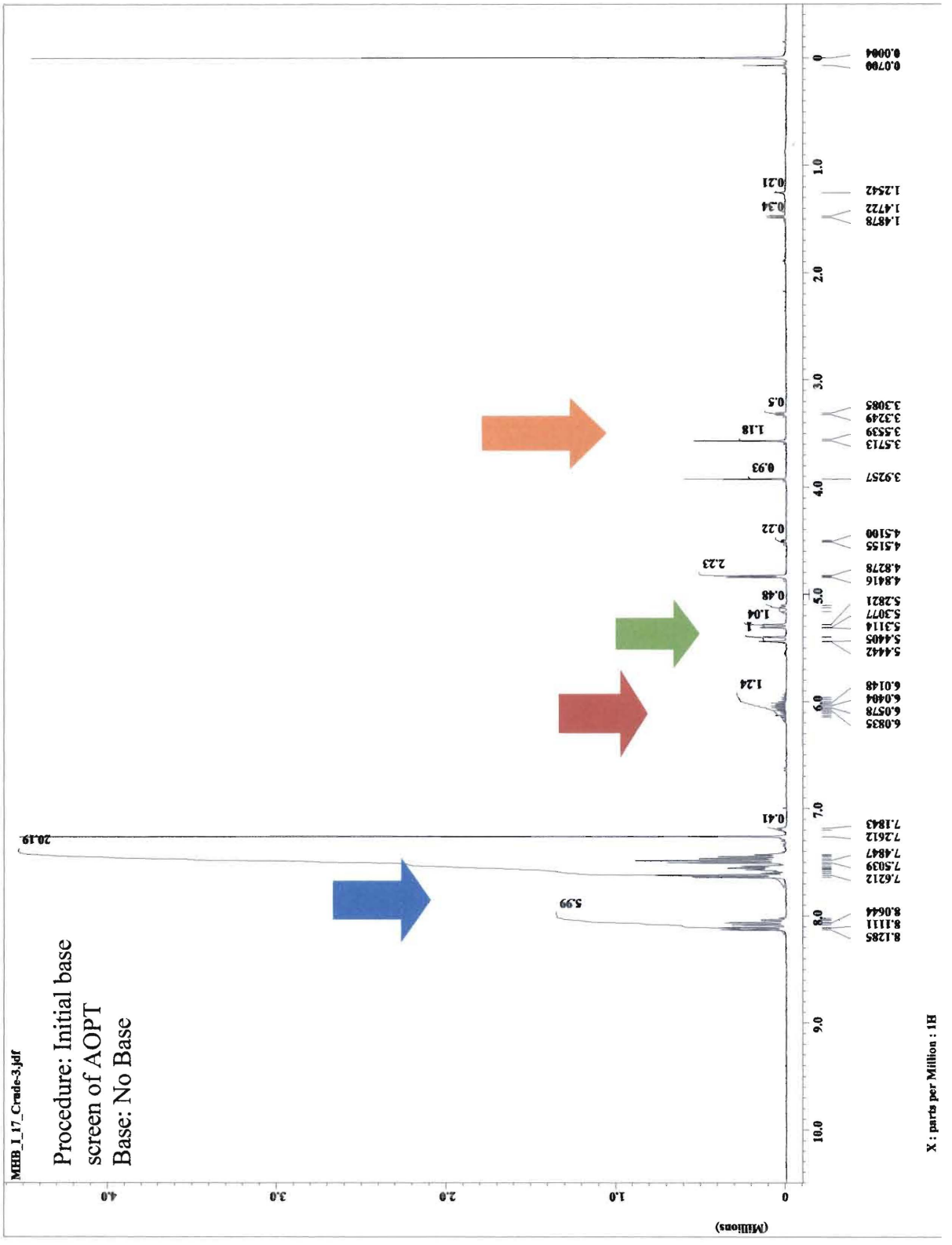

Allyl benzoate
MHB_I_14_Fraction1-3.jdf
X : parts per Million : 1H
(Millions)
0.0003
0.0708
1.5645
0.41
4.8277
4.8414
5.2819
5.3076
5.3973
5.4404
6.0146
6.0403
6.0549
7.2611
7.4287
7.4479
7.4671
7.5688
8.0643
8.0826
2.12
1.01
1.0
2.11
1.04
2.04

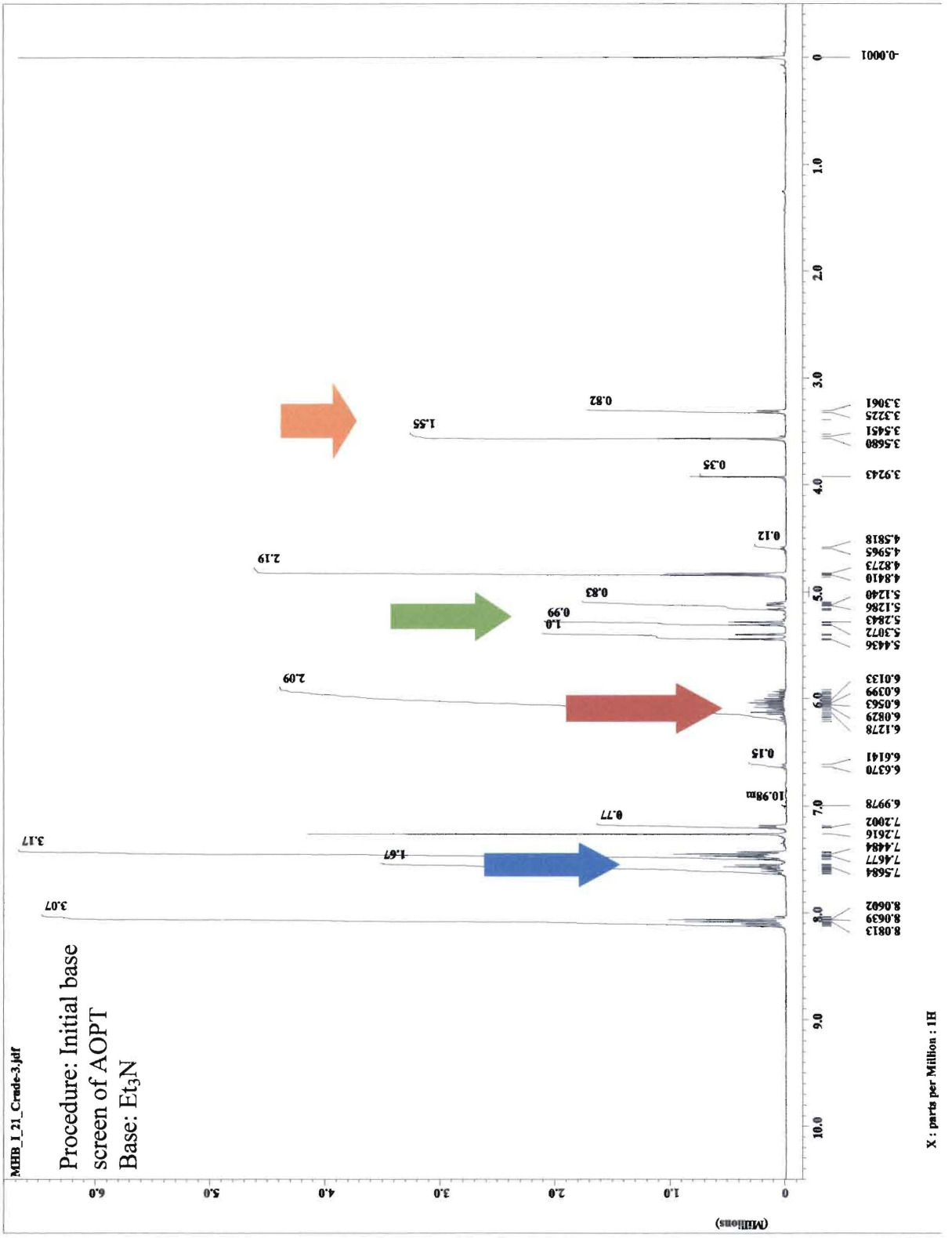
The following series of spectra are examples of the crude NMR results used to determine which base was best suited in the base screen for allylating benzoic acid with **1**. The procedure is described in the experimental section. Each spectra is marked with arrows to highlight diagnostically releveant areas of the spectrum. The blue area allows us to judge the completeness of the reaction, the red and green arrows are good indicators of purity, and the orange arrow can be used to judge how much methyl ester byproduct was also developed.

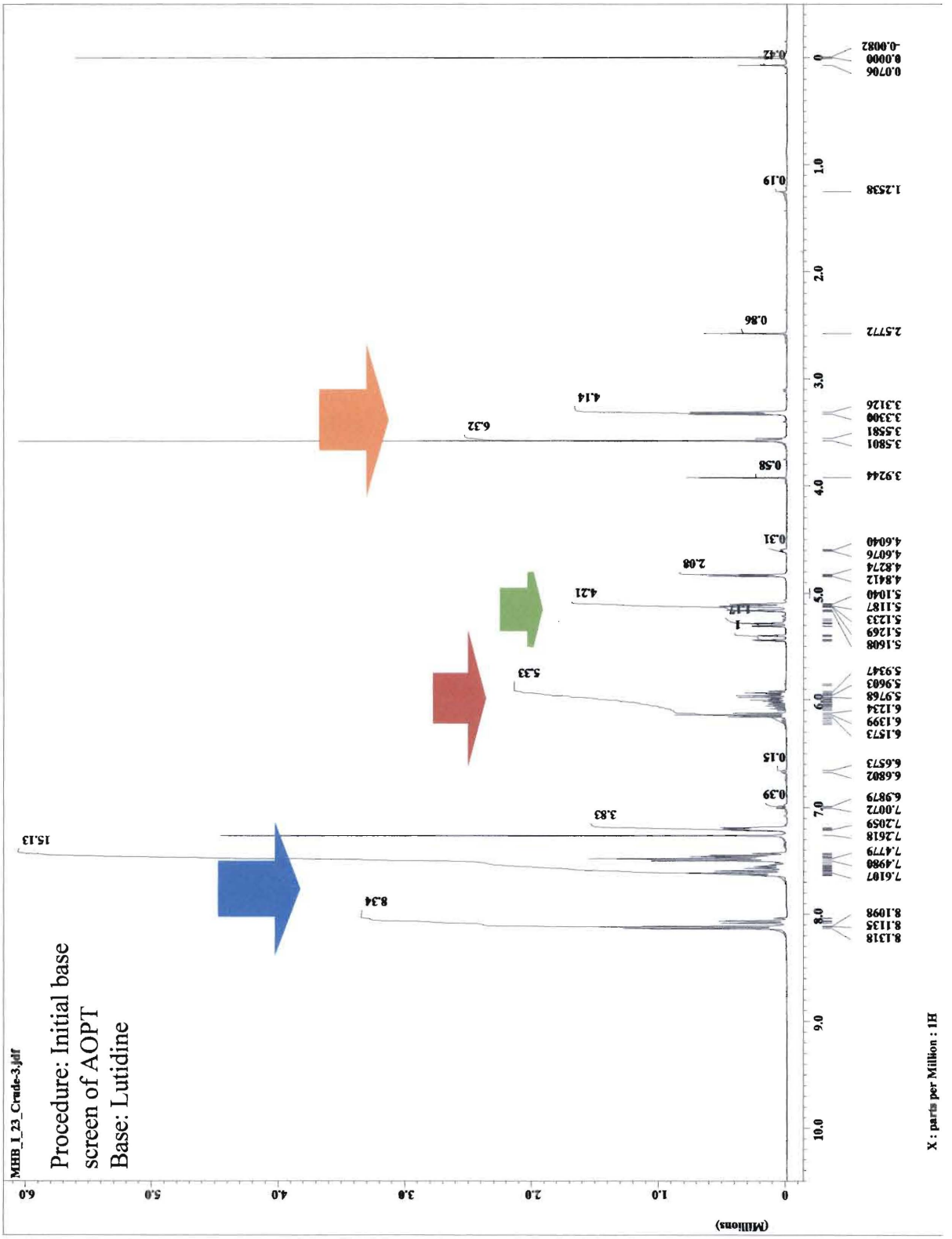

MHB_1_14_Crude-3.jdf
Procedure: Initial base screen of AOPT
Base: K_2CO_3
X : parts per Million : 1H

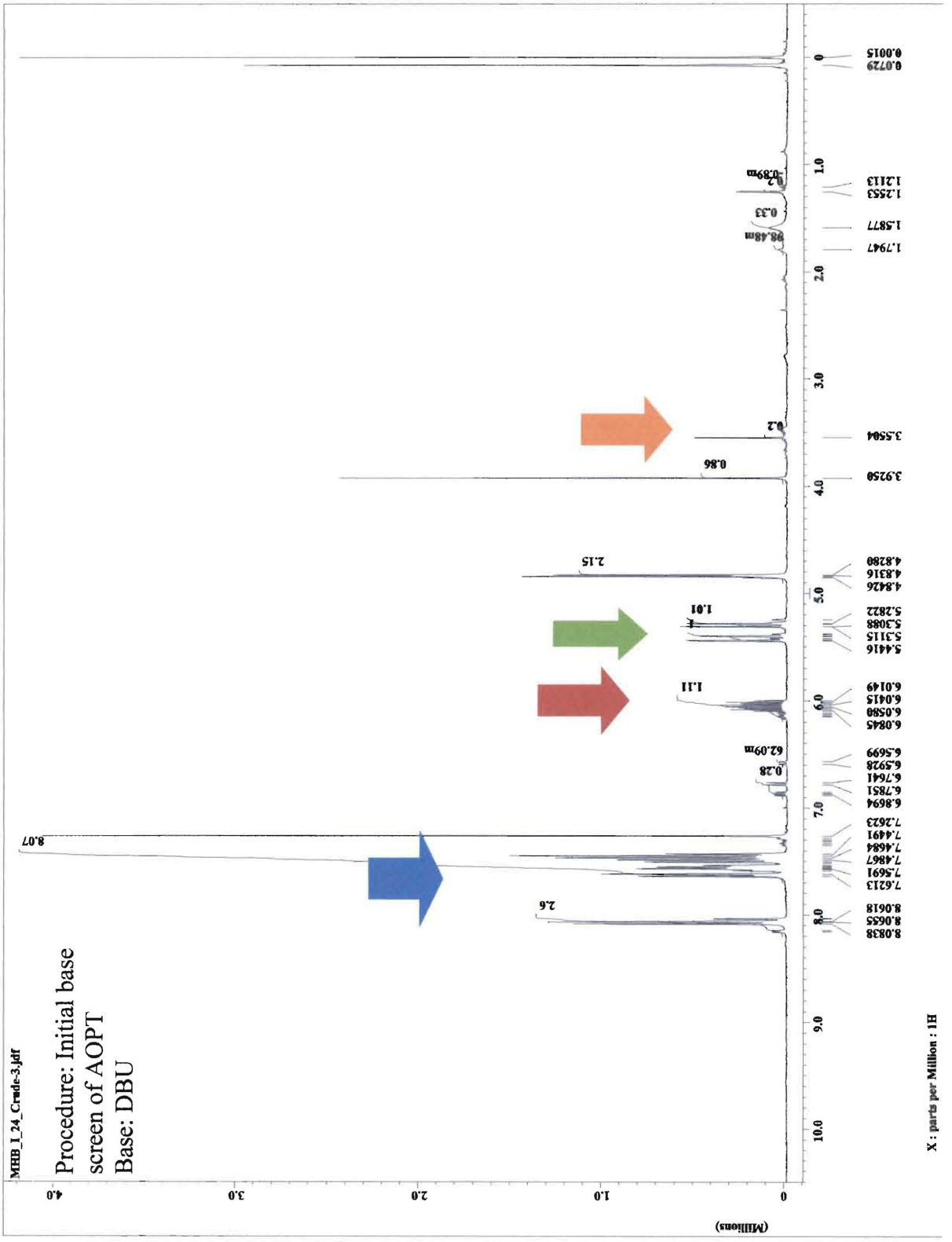

MBB_1_15_Crude-3.jdf
Procedure: Initial base screen of AOPT
Base: $NaHCO_3$
X : parts per Million : 1H
(Millions)

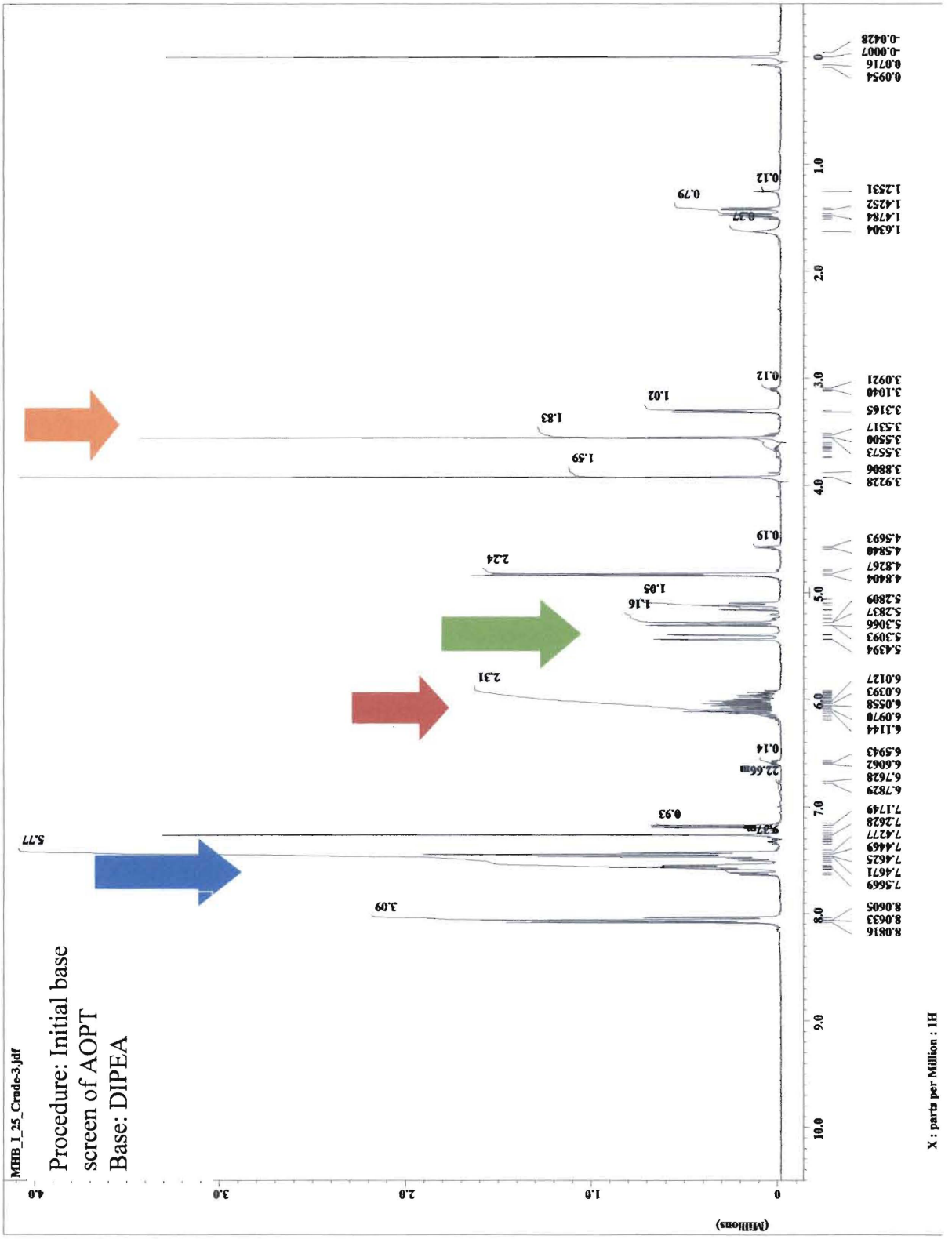

MHB_1_16_Crude-3.jdf
Procedure: Initial base screen of AOPT
Base: MgO
(Millions)
X : parts per Million : 1H


MHB_1_17_Crude-3.jdf
Procedure: Initial base screen of AOPT
Base: No Base
X : parts per Million : 1H

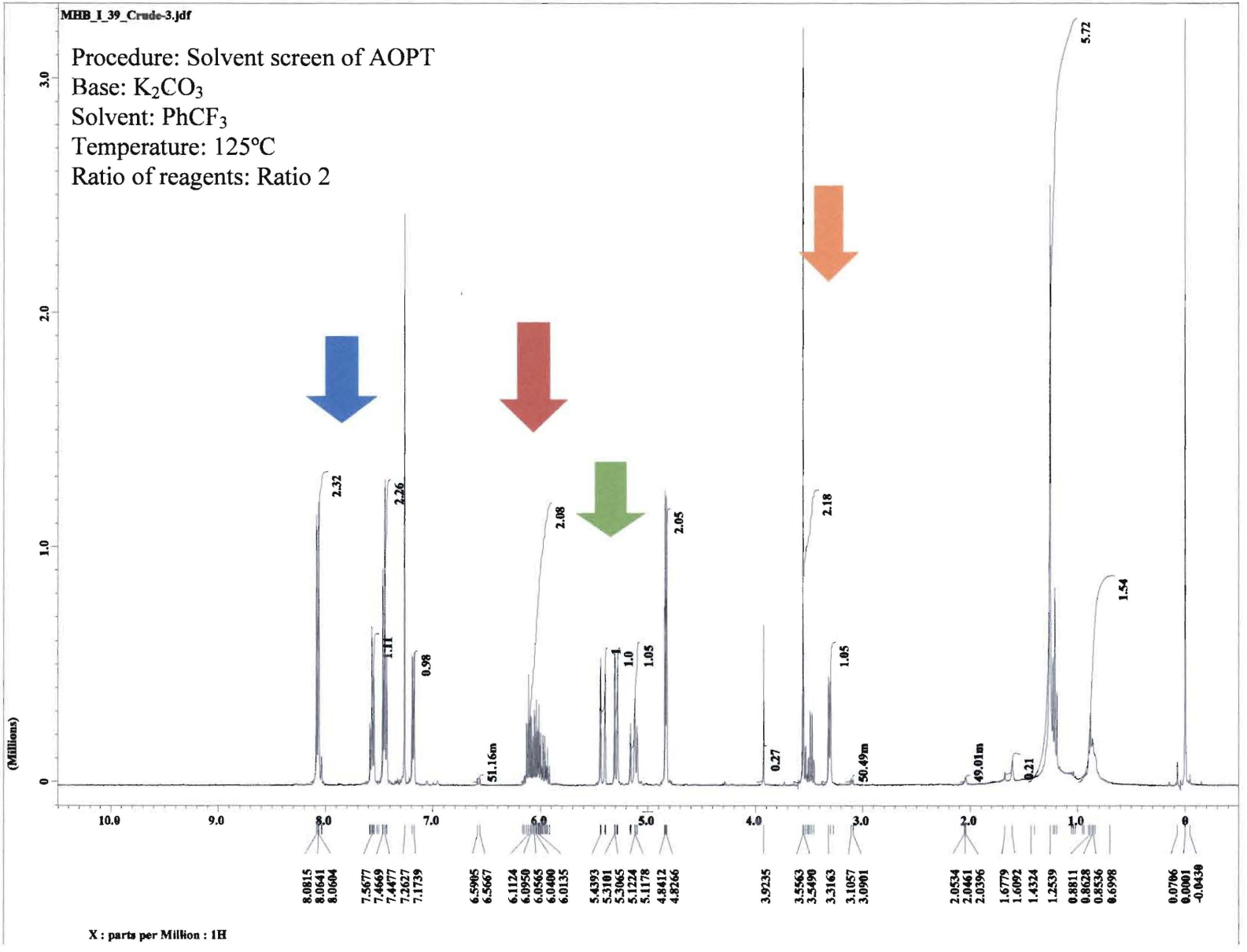

Procedure: Initial base screen of AOPT
Base: Et_3N
MHB_1_21_Crude-3.jdf
X : parts per Million : 1H
(Millions)
3.07
3.17
1.67
0.77
10.98
0.15
2.09
1.0
0.99
0.83
2.19
0.12
0.35
1.55
0.82


MHB_1_23_Crude-3.jdf
Procedure: Initial base screen of AOPT
Base: Lutidine
X : parts per Million : 1H
(Millions)

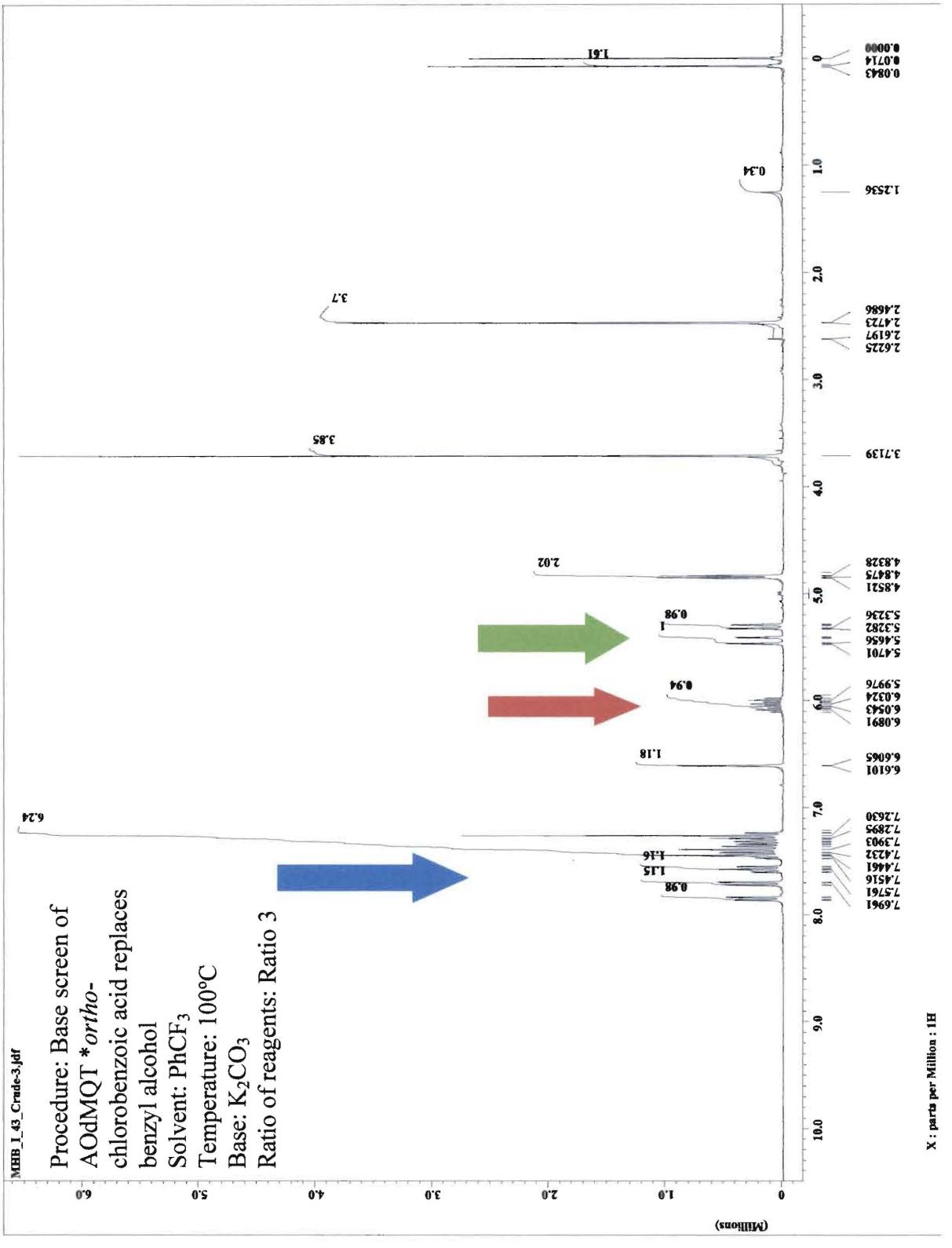

MHB_I_24_Crude-3.jdf
Procedure: Initial base screen of AOPT
Base: DBU
(Millions)
X : parts per Million : 1H

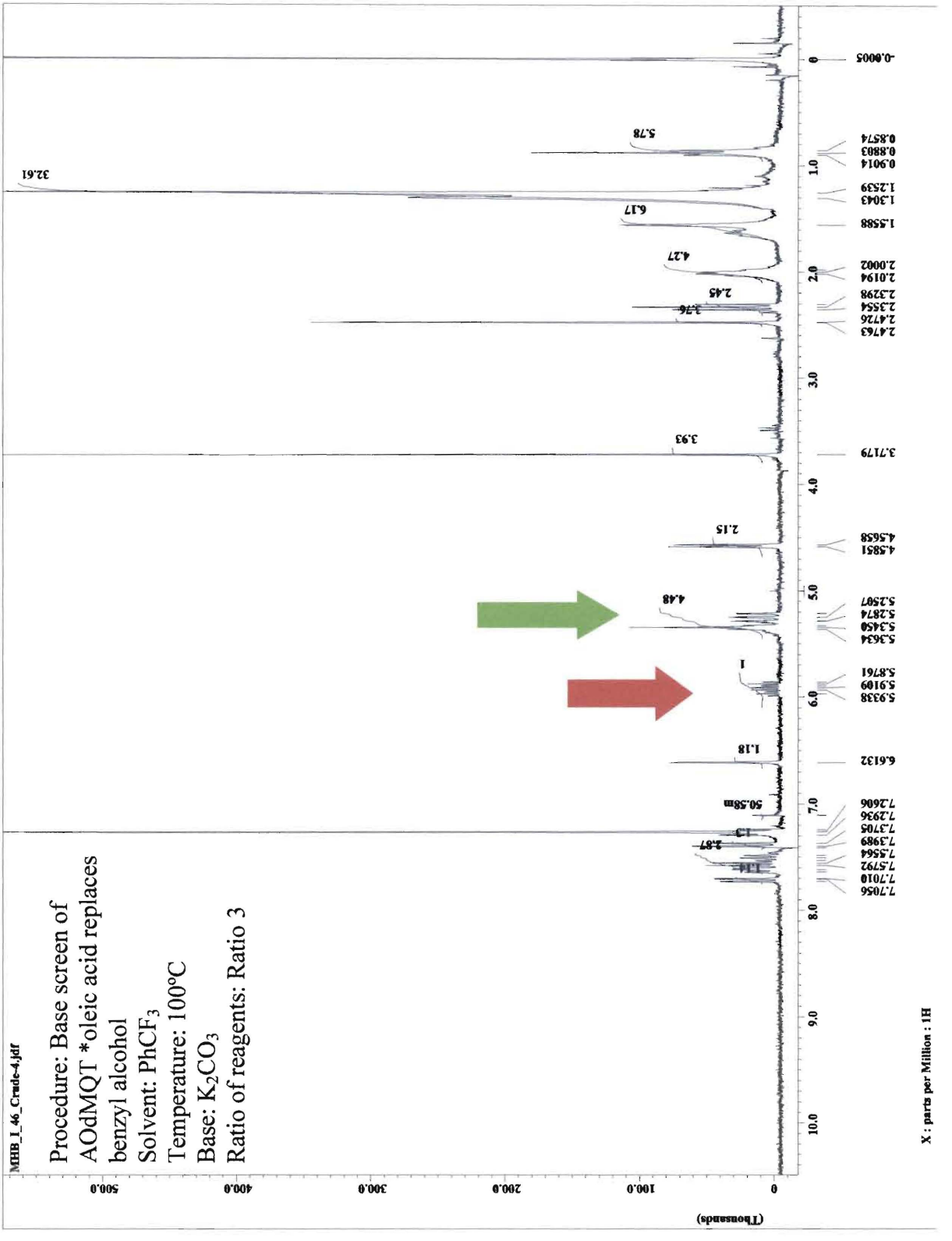

MHB_1_25_Crude-3.jdf
Procedure: Initial base screen of AOPT
Base: DIPEA
(Millions)
X : parts per Million : 1H

The next spectrum, MHB_I_39_Crude, was from the solvent screen portion of the experimental procedures. This reaction again used $PhCF_3$, but at a temperature of 125°C. The base was K_2CO_3, like the spectrum MHB_I_14_Crude. By comparing differences in the relationship of the peaks highlighted by the red and green arrows in each spectrum (14 and 39), it appears that the increased temperature has increased consumption of **1**, but has also increased fragmentation of the desired product. The relationships among peaks in MHB_I_39_Crude suggests that decomposition is occurring to some degree. This degradation is an example of the limitations of increasing temperature, as temperature increases, molecules fall apart more readily.

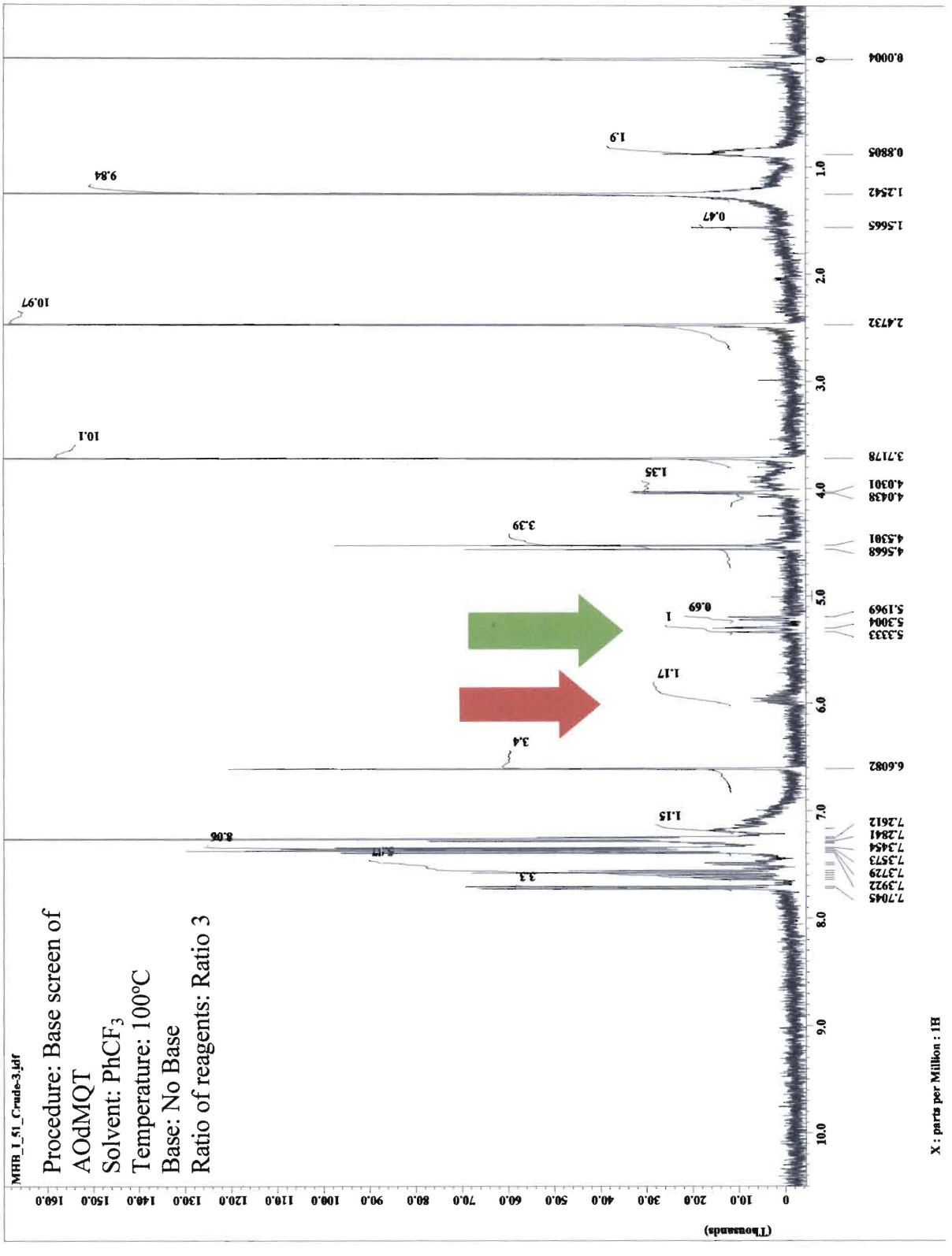

MHB_I_39_Crude-3.jdf
Procedure: Solvent screen of AOPT
Base: K_2CO_3
Solvent: $PhCF_3$
Temperature: 125°C
Ratio of reagents: Ratio 2
(Millions)
X : parts per Million : 1H

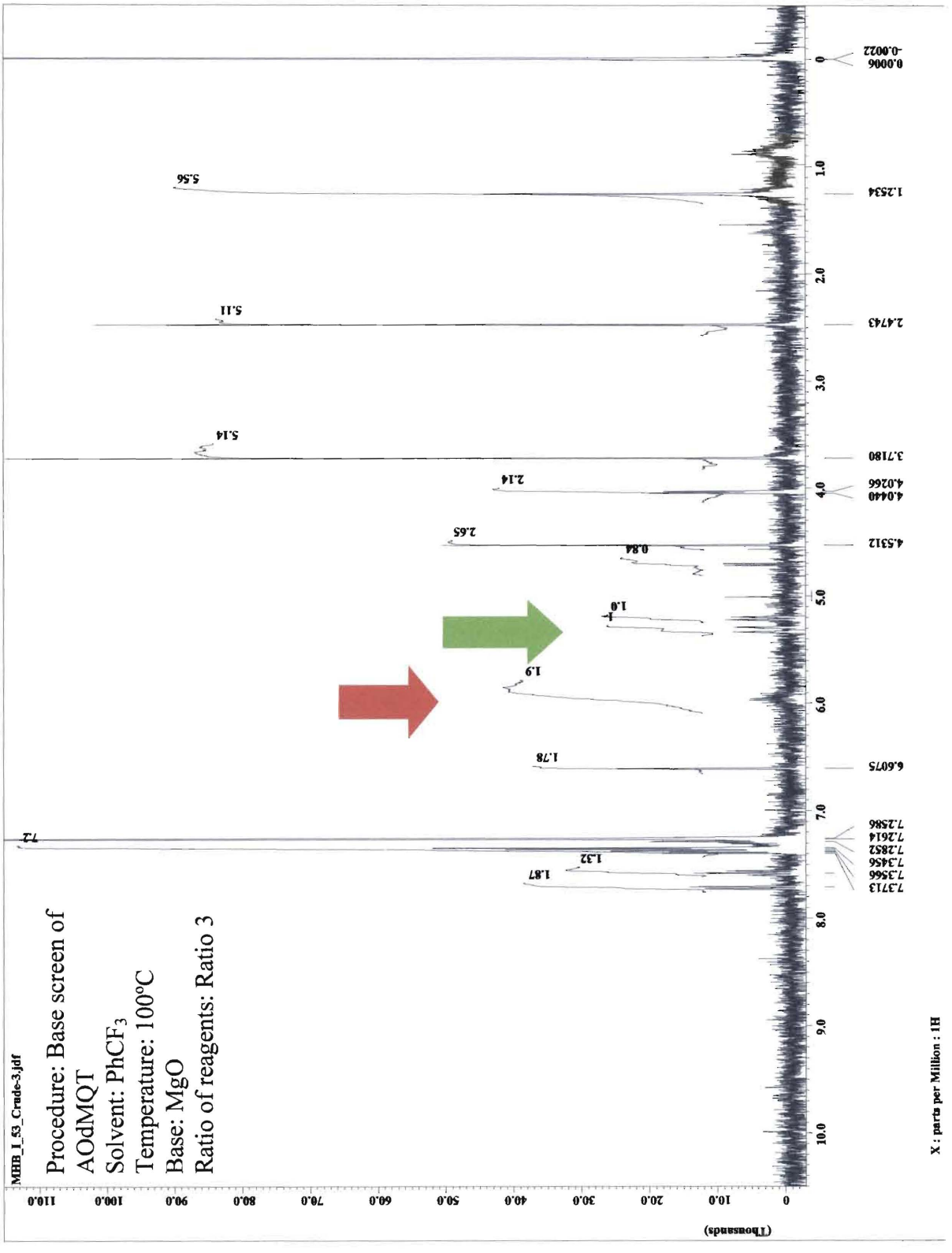
The following spectrums, MHB_I_(43&46)_Crude, are initial tests of **2** with K_2CO_3 as a base and $PhCF_3$ as a solvent at 104°C. MHB_I_43_Crude was performed with *o*-chlorobenzoic acid and MHB_I_46_Crude used oleic acid. The red and green peaks from the above spectra are indicative of the allyl group and are used to judge the success of the reaction.


MHB_I_43_Crude-3.jdf
Procedure: Base screen of AOdMQT *ortho-chlorobenzoic acid replaces benzyl alcohol
Solvent: $PhCF_3$
Temperature: 100°C
Base: K_2CO_3
Ratio of reagents: Ratio 3
X : parts per Million : 1H


MHB_I_46_Crude-4.jdf
Procedure: Base screen of AOdMQT *oleic acid replaces benzyl alcohol
Solvent: $PhCF_3$
Temperature: 100°C
Base: K_2CO_3
Ratio of reagents: Ratio 3
(Thousands)
X : parts per Million : 1H

The following spectra are crude results of an initial base screen of AOdMQT The procedure is explained above. Again, the red and green arrows are indicative of the allyl group and are used to judge completeness of the reaction and ratios of desired product to byproduct produced.


MHB_1_51_Crude-3.jdf
Procedure: Base screen of AOdMQT
Solvent: $PhCF_3$
Temperature: 100°C
Base: No Base
Ratio of reagents: Ratio 3
(Thousands)
X : parts per Million : 1H
8.0004
0.8805
1.2542
1.5665
2.4732
3.7178
4.0301
4.0438
4.5301
4.5668
5.1969
5.3004
5.3333
6.6082
7.2612
7.2841
7.3454
7.3573
7.3729
7.3922
7.7045
10.97
9.84
1.9
0.47
10.1
1.35
3.39
0.69
1
1.17
3.4
1.15
8.06
3.3


MHB_I_53_Crude-3.jdf
Procedure: Base screen of AOdMQT
Solvent: PhCF3
Temperature: 100°C
Base: MgO
Ratio of reagents: Ratio 3
(Thousands)
X : parts per Million : 1H
7.2
1.87
1.32
1.78
1.9
1.0
0.84
2.65
2.14
5.14
5.11
5.56
7.3713
7.3566
7.3456
7.2852
7.2614
7.2586
6.6075
4.5312
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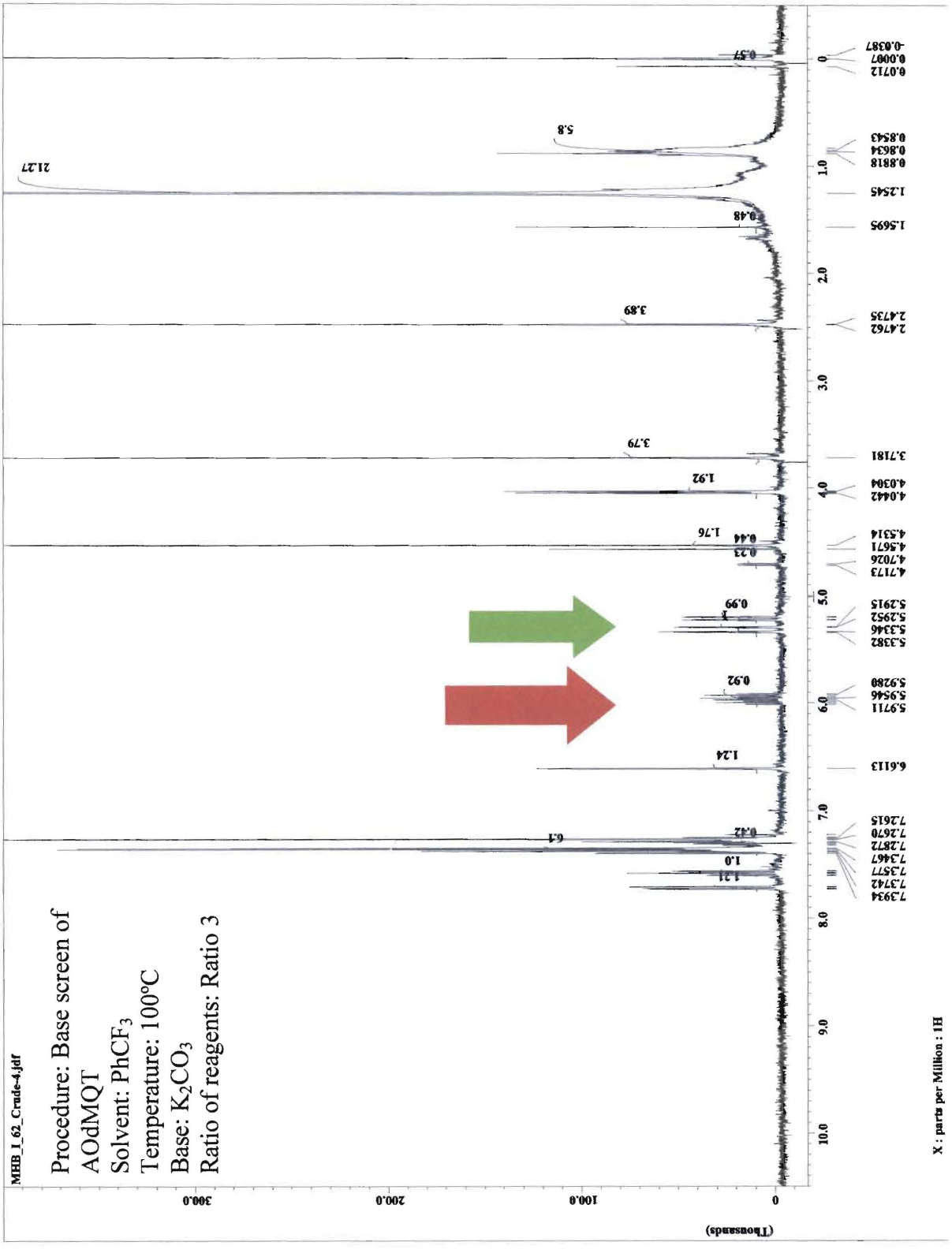
4.0266
3.7180
2.4743
1.2534
0.0006
-0.0022


MHB_1_62_Crude-4.jdf
Procedure: Base screen of AOdMQT
Solvent: $PhCF_3$
Temperature: 100°C
Base: K_2CO_3
Ratio of reagents: Ratio 3
(Thousands)
X : parts per Million : 1H

References

[1] Wuts, P.G.M.; Greene, T.W. Greene's Protective Groups in Organic Synthesis, 4th Ed. John Wiley & Sons: Hoboken, NJ, 2007.

[2] Brummond, K.M.; Sang-phyo, H. A Formal Total Synthesis of (-)-FR901483, Using a Tandem Cationic Aza-Cope Rearrangement/Mannich Cyclization Approach. *J. Org. Chem.* **2005**, *70*, 907-916.

[3] Van Hijfte, L.; Little, R.D.; Intramolecular 1,3-Diyl Trapping Reactions. A Formal Total Synthesis of (f)-Coriolin. *J. Org. Chem.* **1985**, *50*, 3940-3942.

[4] Cruzado, C.; Bernabe, M.; Martin-Lomas, M. Regioselectivity of tributyltin ether mediated alkylations. A tin-119 and carbon-13 NMR study. *J. Org. Chem.* **1989**, *54*, 465.

[5] Salomon, C.J.; Mata, R.G.; Mascaretti, O.A. Scope and Mechanism of Deprotection of Carboxylic Esters by Bis(tributyltine) Oxide. *J. Org. Chem.* **1994**, *59*, 7259-7266.

[6] Fukuzawa, A.; Sato, H.; Masamune, T. Synthesis of (±)-prepinnaterpene, a bromoditerpene from the red alga *Laurencia pinnata* Yamada. *Tetrahedron Lett.* **1987**, *28*, 4303-4306.

[7] Heathcock, C.H.; Ratcliffe, R. A Stereoselective Total Synthesis of the Guaiazulenic Sesquiterpenoids a-Bulnesene and Bulnesol. *J. Am. Chem. Soc.* **1971**, *93*, 1746-1757.

[8] Goodman, L.; Christensen, J.E. Preparation of 6-Acetamido-1,2,3,4-tetra-O-acetyl-6-deoxy-L- Idothiapyranose. *J. Org. Chem.* **1964**, *29*, 1787-1790.

[9] Angyal, S.J.; James, K. Oxidative demethylation with chromium trioxide in acetic acid. *Carbohydrate. Res.* **1970**, *12*, 147.

[10] Poon, K.W.C.; House, S.E.; Dudley, G.B. A Bench Stable Organic Salt for the Benzylation of Alcohols. *Synlett.* **2005**, *20*, 3142-3144.

[11] Poon, K.W.C.; Albiniak, P.A.; Dudley, G.B. Protection of Alcohols Using 2-Benzyloxy-1-Methylpyridinium Trifluoromethanesulfonate: Methyl (*R*)-(--)-3-Benzyloxy-2-Methyl Propanoate. *Org. Synth.* **2007**, *84*, 295-305.

[12] Albiniak, P.A.; Dudley, G.B. New Reagents for the Synthesis of Arylmethyl Ethers and Esters. *Synlett.* **2010**, *6*, 841-851

[13] Poon, K.W.C.; Dudley, G.B. Mix-and-Heat Benzylation of Alcohols Using Bench-Stable Pyridinium Salt. *J. Org. Chem.* **2006**, *71*, 3923-3927.

[14] Stecko, S.; Solecka, J. Synthesis of casuarine-related derivatives via 1,3-dipolar cycloaddition between a cyclic nitrone and an unsaturated γ-lactone. *Carbohydrate Res.* **2009**, *344*, 167.

[15] Legeay, J.C.; Langlois, N. Nitrone [2+3]-Cycloadditions in Stereocontrolled Synthesis of a Potent Proteasome Inhibitor: (−)-Omuralide. *J. Org. Chem.* **2007**, *72*, 10108.

[16] Lango, C.M.; Wei, Y.; Roberts, M.F.; Miller, S.J. Asymmetric Syntheses of l,l- and l,d-Di-myo-inositol-1,1'-phosphate and their Behavior as Stabilizers of Enzyme Activity at Extreme Temperatures. *Angew. Chem. Int. Ed. Engl.* **2009**, *48*, 4158.

[17] Tummatorn, J.; Albiniak, P.A.; Dudley, G.B. Synthesis of Benzyl esters Using 2-Benzyloxy-1-methylpyridinium Triflate. *J. Org. Chem.* 2007, *72*, 8962-8964.

[18] Albiniak, P.A.; Dudley, G.B. Thermally generated phenylcarbenium ions: acid-free and self-quenching Friedel-Crafts reactions. *Tetrahedron Letters.* **2007**, *48*, 8097-8100.

[19] Tayyebeh Bakhshi, current group member.

[20] Anna Salvati, current group member.

[21] Nwoye, E. O.; Dudley, G. B. Synthesis of para-methoxybenzyl (PMB) ethers under neutral conditions. *Chem. Commun.* **2007**, 1436.

[22] Albiniak, P. A.; Amisial, S.M.; Dudley, G.B.; Hernandez, J.P.; House, S.E.; Matthews, M.E.; Nwoye, E.O.; Reilly, M.K.; Tlais, S.F. Stable Oxypyridinium Triflate (OPT) Salts for the Synthesis of Halobenzyl Ethers. *Synth. Commun.* **2008**, *38*, 656.

[23] Dahlen, A.; Sundgren, A.; Lahmann, M.; Oscaron, S.; Hilmersson, G. SmI_2/Water/Amine Mediates Cleavage of Allyl Ether Protected Alcohols: Application in Carbohydrate Synthesis and Mechanistic Considerations. *Organic Letters.* **2003**, *5 (22)*, 4085-4088.

[24] Friedrich-Bochnitschek, S.; Waldmann, H.; Kunz, H. Allyl Esters as Carboxy Protecting Groups in the Synthesis of *O*-Glycopeptides. *J. Org. Chem.* **1989**, *54*, 751-756.

[25] Jeffrey, P.D.; McCombie, S.W. Homogeneous, Palladium(0)-Catalyzed Exchange Deprotection of Allylic Esters, Carbonates, and Carbamates. *J. Org. Chem.* **1982**, *47*, 587.

[26] Lakhmiri, R.; Lhoste, P.; Sinou, D. Allyl ethyl carbonate/palladium (0), a new system for the one step conversion of alcohols into allyl ethers under neutral conditions. *Tetrahedron Lett.* **1989**, *30*, 8847.
[27] Yin, H.; Franck, R.W.; Chen, S.-L.; Quigley, G.J.; todaro, T. A convergent Synthetic Approach to a Chiral, Nonracemic CDEF Analogue of Nogalamvcin. *J. Org. Chem.* **1992**, *57*, 644-651.
[28] Jager, V. *The Tenth International Congress of Heterocyclic Chemistry*, **1985**.
[29] Kunz, H.; waldmann, H.; Unverzagt, C. Allyl ester as temporary protecting group for the β-carboxyl function of aspartic acid. *Int. J. Pept. Protein res.* **1985**, *54*, 751.
[30] Waddel, S.T.; Santorelli, G.M. Mild prepatation of cephalosporin allyl and p-methoxybenzyl esters using diaoalkanes. *Tetrahedron Lett.* **1996**, *37*, 1971.
[31] Gigg, J.; Gigg, R. The allyl ether as a protecting group in carbohydrate chemistry. *J. Chem. Soc. C.* **1966**, *0*, 86.
[32] Corey, E.J.; Suggs, J.W. Selective Cleavage of Allyl ethers under Mild Conditions by Transition Metal Reagents. *J. Org. Chem.* **1973**, *38*, 3224.
[33] Dahlén, A.; Sundgren, A.; Lahmann, M.; Oscarson, S.; hilmersson, G. SmI2/Water/Amine Mediates Cleavage of Allyl Ether Protected Alcohols: Application in Carbohydrate Synthesis and Mechanistic Considerations. *Org. Lett.* **2003**, *5*, 4085-4088.
[34] Previous work of someone in Albiniak research group.